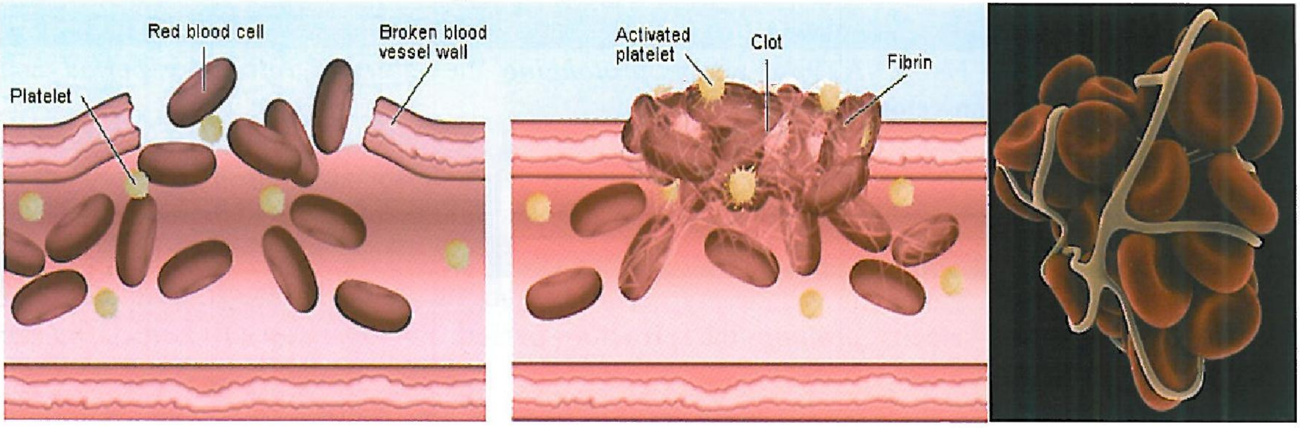
Blood Coagulation

➢ Introduction:-

- *In normal situation* there is a **delicate balance** that *prevents* **thrombosis** and **hemorrhage**.
- **Disorders of coagulation** ***can lead to*** an ***increased*** **risk of bleeding (hemorrhage)** ***or*** **obstructive clotting (thrombosis)**.
- *Inside the vascular system* **the blood *must be*** remain fluid ***but*** when exposed to **non-endothelial surface** outside the vascular system, it clots quickly as in case of vascular injury. ***When*** **intravascular thrombi *occur***, a system of fibrinolysis is activated to restore fluidity.

➢ Main Steps of Clot Formation:-

1: **Vasoconstriction (VC)**; to decrease blood flow in injured area.
2: **Platelet adheres** to macromolecules in the subendothelial regions of the injured blood vessels.
3: **Release of intracellular granules** containing chemical mediators.
4: **Platelets aggregate** to form the primary haemostatic plug.
5: **Activation of plasma coagulation factors**, leading to generation of thrombin which catalysis the conversion of fibrinogen to fibrin.



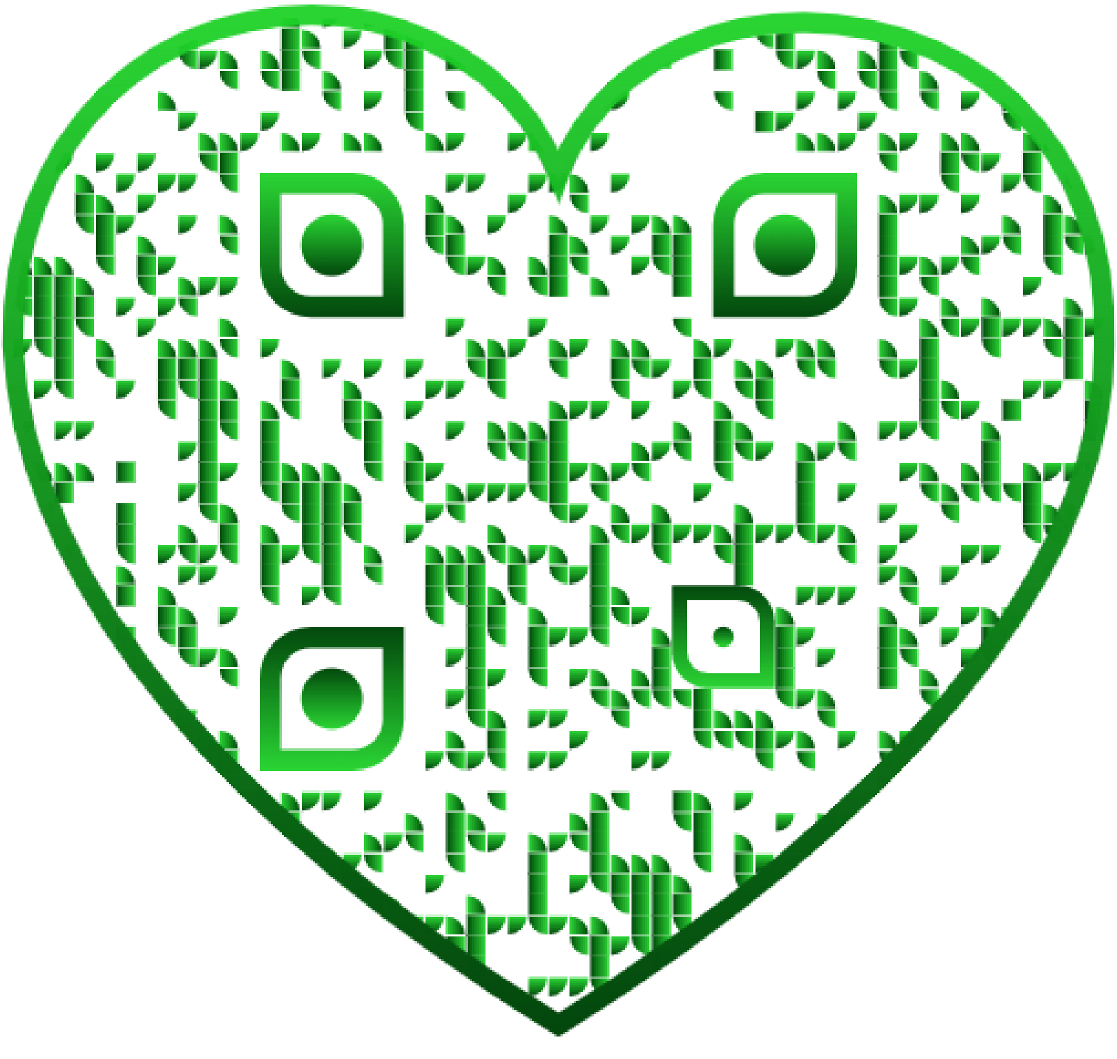
➢ Overview of Platelet Physiology:-

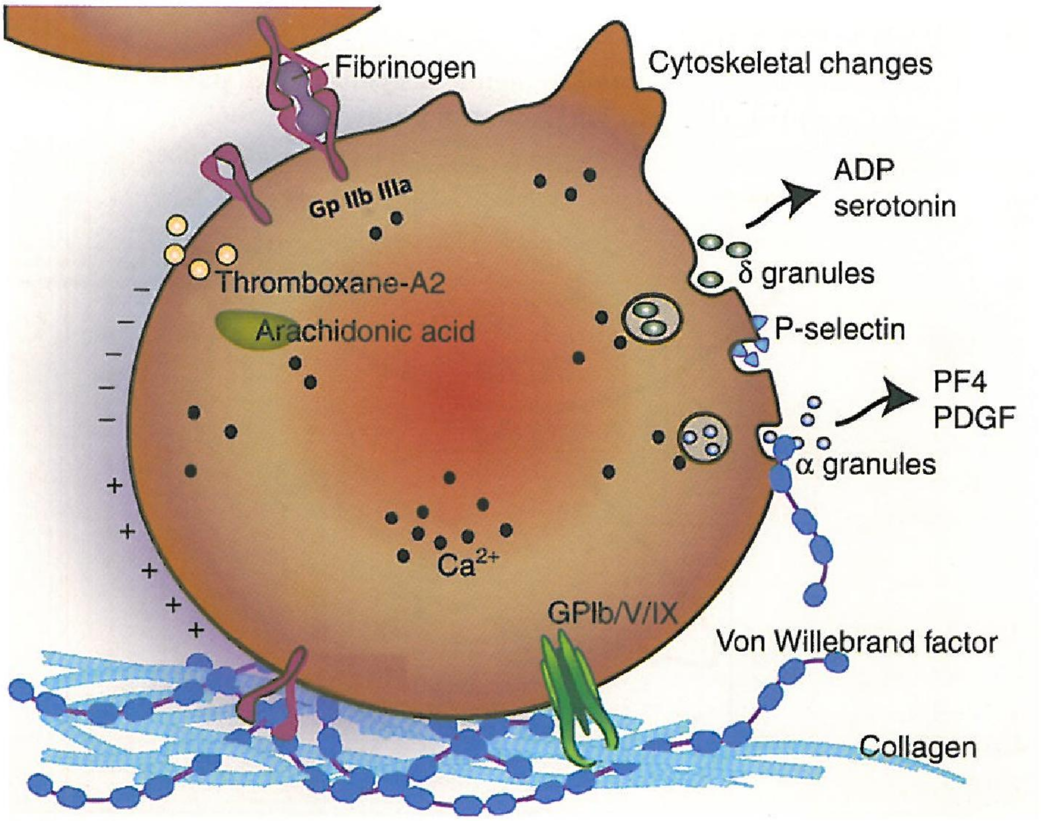
- Introduction;

- Platelets were discovered by *Giulio Bizzozero* in 1882.
- They are primarily associated with ***hemostasis***, which is to ***initiate*** **blood coagulation**, ***but*** hemostasis or blood coagulation is not the sole function of platelets.
- **Platelet activity** is ***associated with*** the **initiation** of **coagulation cascades**.
- ***Damage in blood vessel*** makes the subendothelial surface the primary ***target site*** of **platelet action**, where it establishes the hemostasis.

- Structure;

- **Platelet plasma membrane** (phospholipid bilayer); is the site of expression of various **surface receptors** and **lipid rafts** which helps in signalling and intracellular trafficking.
- Platelets have **two major storage granules**; α and dense granules;
  - 1: **α granules**; which ***play a role*** in **multiple functions**; coagulation, inflammation, atherosclerosis, antimicrobial host defense, angiogenesis, wound repair and tumorigenesis. α granule contains proteins (e.g., Glycoprotein IIb/IIIa; GPIIbIIIa, fibrinogen and Von Willebrand factor; vWf) which initiate the coagulation cascades.
  - 2: **Dense granules *or* delta (δ) granules**; which are secreted during platelet activation; these include catecholamines, serotonin, calcium, adenosine diphosphate (ADP) and adenosine triphosphate (ATP). ADP is a weak platelet agonist, triggering platelet shape change, granule release and aggregation.





- Platelet Response to Vascular Injury;

1: **Resting Platelets**;

- Platelets act as vascular sentries, monitoring the integrity of the vascular endothelium.
- In the absence of injury, resting platelets circulate freely, because the balance of chemical signals indicates that the vascular system is not damaged.

2: **Platelet Adhesion**;

- ***When the endothelium is injured***; Glycoprotein Ib/V/IX Complex and subendothelial compounds like Von Willebrand factor (vWf) and collagen interact with each other to platelet adhesion to exposed subendothelial surface of damaged endothelium.

3: **Platelets Activation**;

- Receptors on the surface of the adhering platelets are activated by the collagen.
- This causes ***morphologic changes*** in platelets (from spherical to stellate) and the release of platelet granules containing chemical mediators, such as;
    - Adenosine diphosphate (ADP), serotonin, platelet-activating factor (PAF), Von Willebrand factor (vWf), platelet factor 4 and thromboxane A_2 (TXA_2).
- These signaling molecules bind to receptors in the outer membrane of resting platelets circulating nearby ⇨ platelets become activated and start to aggregate.
- ***During shape change***, platelet fibrinogen receptors (GPIIb/IIIa) are exposed and activated and platelet-platelet aggregation is initiated.

4: **Platelet Aggregation**;

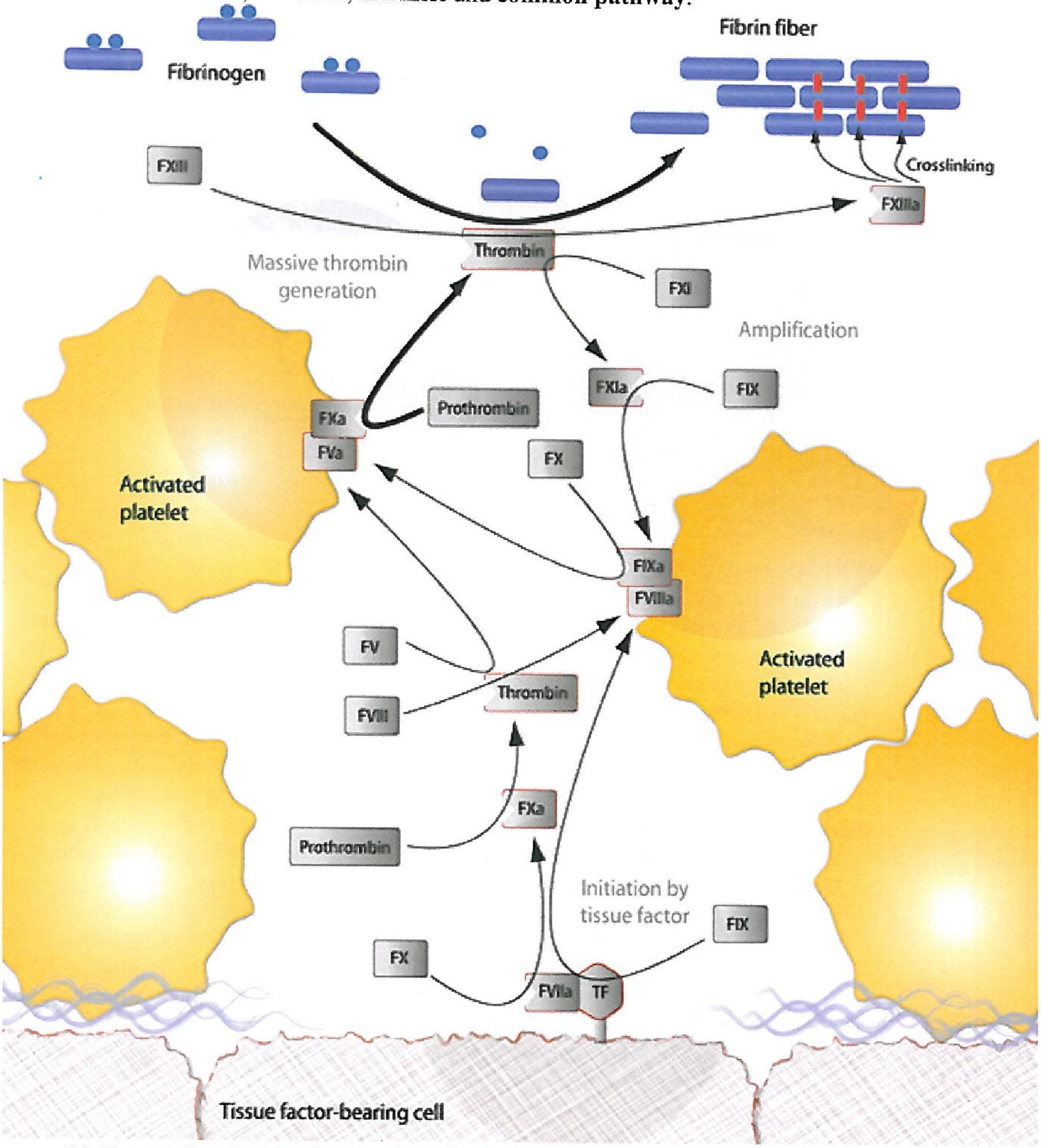
- The chemical mediator activate a G-protein (Gq) receptor, ⇨ ↑ intracellular Ca^{2+}.
- The Ca^{2+} activates protein kinase C ⇨ which activates phospholipase A2 (PLA_2).
- PLA_2 then modifies the integrin membrane glycoprotein IIb/IIIa, increasing its affinity to bind fibrinogen ⇨ platelets aggregate.

- *Notes*;

- Arachidonic acid-thromboxane (TXA_2) pathway is an important platelet activation pathway.
- Adenosine diphosphate (ADP) is another important platelet activator. P2Y12, an ADP specific receptor, which can activate GPIIb/IIIa receptor, leads to platelet aggregation.
- Prostacyclin and nitric oxide, are synthesized by endothelial cells and act as inhibitors of platelet aggregation.
    - Prostacyclin (PGI_2) acts by binding to platelet membrane receptors ⇨ ↑ cyclic adenosine monophosphate (cAMP) ⇨ ↓ intracellular Ca^{2+} ⇨ ↓ platelet activation.
    - Damaged endothelial cells ⇨ synthesize less prostacyclin than ⇨ ↑ platelet activation.

➢ Coagulation Cascade:-

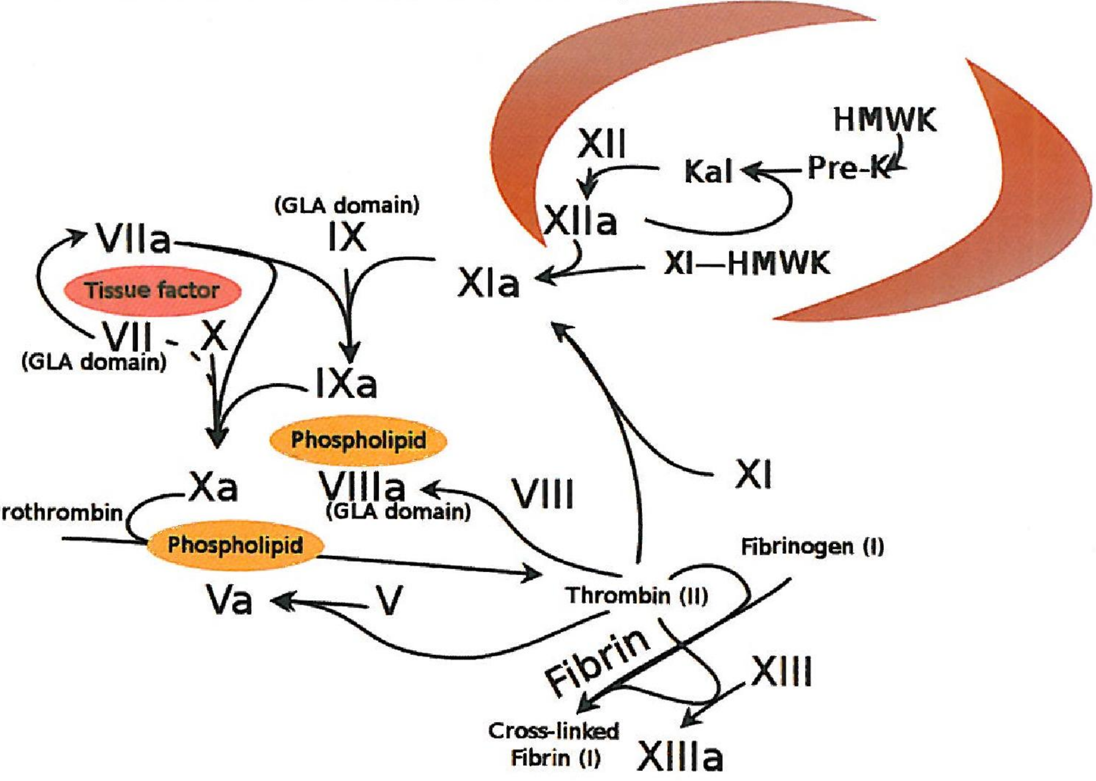
- The coagulation cascade (***secondary*** **hemostasis)** has ***three*** **pathways** which lead to fibrin formation; **extrinsic**, **intrinsic** and **common pathway**.


Fibrinogen
Fibrin fiber
Crosslinking
FXIII
FXIIIa
Thrombin
Massive thrombin generation
FXI
Amplification
FXIa
FIX
Prothrombin
FXa
FVa
Activated platelet
FX
FIXa
FVIIIa
FV
FVIII
Thrombin
Activated platelet
FXa
Prothrombin
Initiation by tissue factor
FIX
FX
FVIIa
TF
Tissue factor-bearing cell

A) Tissue Factor Pathway (Extrinsic);

- **Tissue factor (TF)**; is a protein present in subendothelial tissue.
- ***The main role*** of the **tissue factor pathway** is to ***generate*** a **minor amount of thrombin**.
- TF itself has no enzymatic function, but serves as a **cofactor** and ***facilitates*** **rapid auto-activation of factor VII**.
- ***The process includes the following steps***:
  1) After damage of blood vessel; Factor VII (FVII) leaves the circulation and comes into contact with tissue factor (TF) forming an activated complex (TF-FVIIa).
  2) TF-FVIIa activates factor IX (FIX) and factor X (FX) to FIXa and FXa.
  3) FXa and its co-factor FVa, activates prothrombin to thrombin.
  4) Thrombin then activates other components of the coagulation cascade.

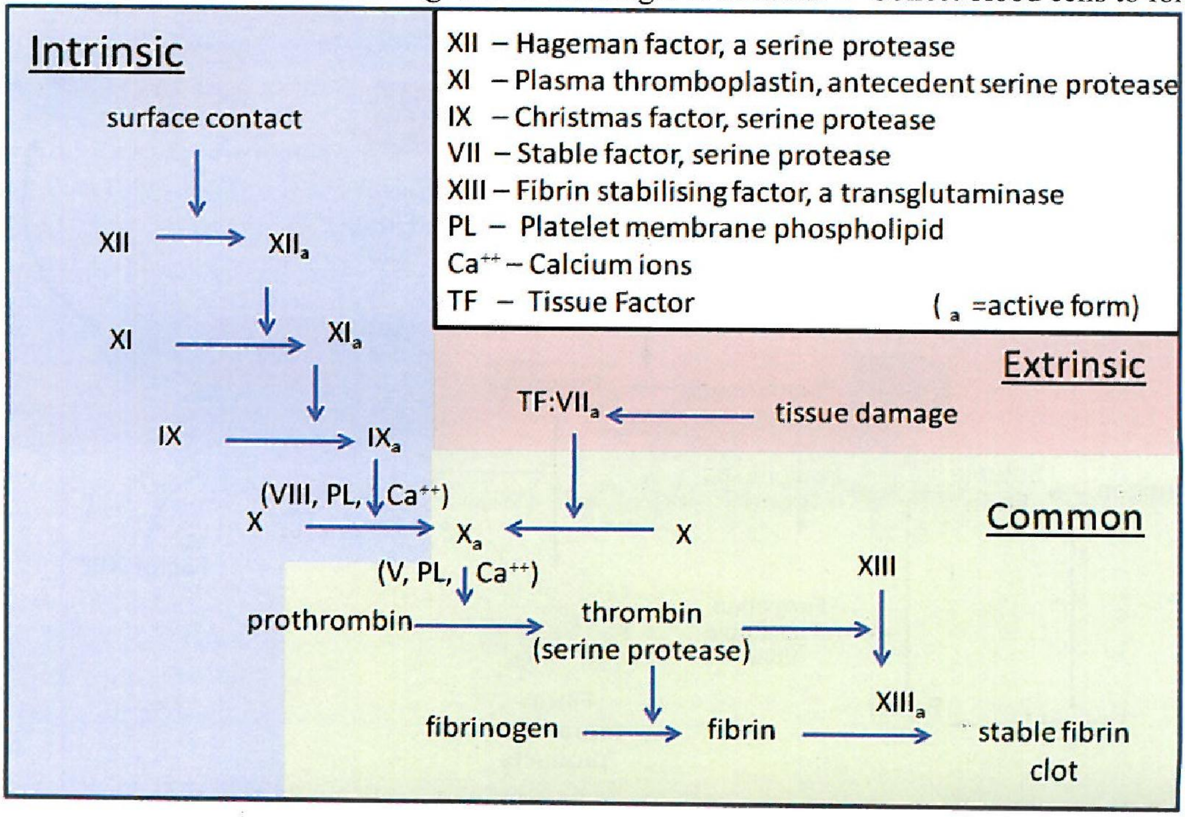
B) Contact Activation Pathway (Intrinsic);


HMWK
XII
Kal
Pre-K
XIIa
XI—HMWK
XIa
(GLA domain)
IX
VIIa
Tissue factor
VII - X
(GLA domain)
IXa
Phospholipid
Xa
VIIIa
(GLA domain)
VIII
XI
Prothrombin
Phospholipid
Fibrinogen (I)
Thrombin (II)
Va
V
Fibrin
XIII
Cross-linked
Fibrin (I)
XIIIa

- The **contact activation pathway *begins*** with formation of the primary complex on collagen by high-molecular-weight kininogen (HMWK), prekallikrein and FXII.
- Prekallikrein is converted to kallikrein and FXII becomes FXIIa.
- FXIIa converts FXI into FXIa.
- Factor XIa activates FIX, which activates FX to FXa.

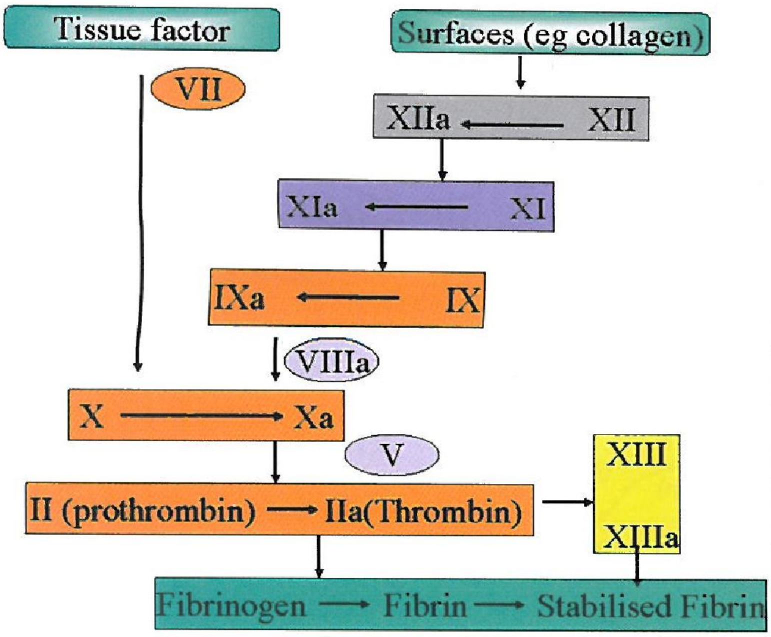
C) Common Pathway;

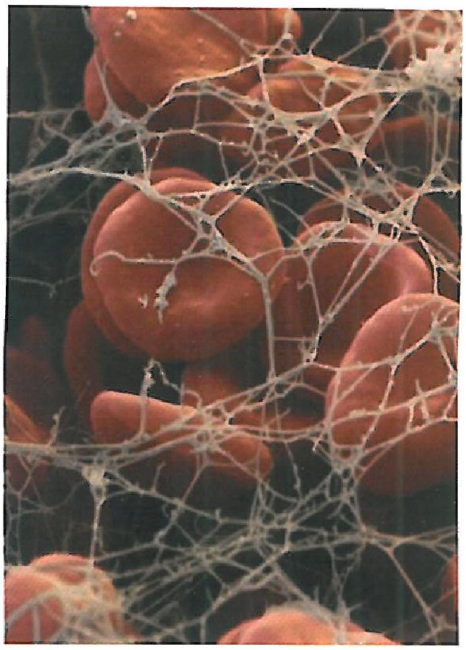
- Formation of FXa to the formation of active thrombin from prothrombin.
- Thrombin converts fibrinogen to fibrin.
- Fibrin monomers bind together to form a gel of network ⇨ Collect blood cells to form clot.


Intrinsic
surface contact
XII
XII_a
XI
XI_a
IX
IX_a
(VIII, PL, Ca^{++})
X
X_a
X
Extrinsic
$TF:VII_a$
tissue damage
Common
(V, PL, Ca^{++})
prothrombin
thrombin
(serine protease)
XIII
$XIII_a$
fibrinogen
fibrin
stable fibrin clot

XII – Hageman factor, a serine protease
XI – Plasma thromboplastin, antecedent serine protease
IX – Christmas factor, serine protease
VII – Stable factor, serine protease
XIII – Fibrin stabilising factor, a transglutaminase
PL – Platelet membrane phospholipid
Ca^{++} – Calcium ions
TF – Tissue Factor
($_a$ =active form)

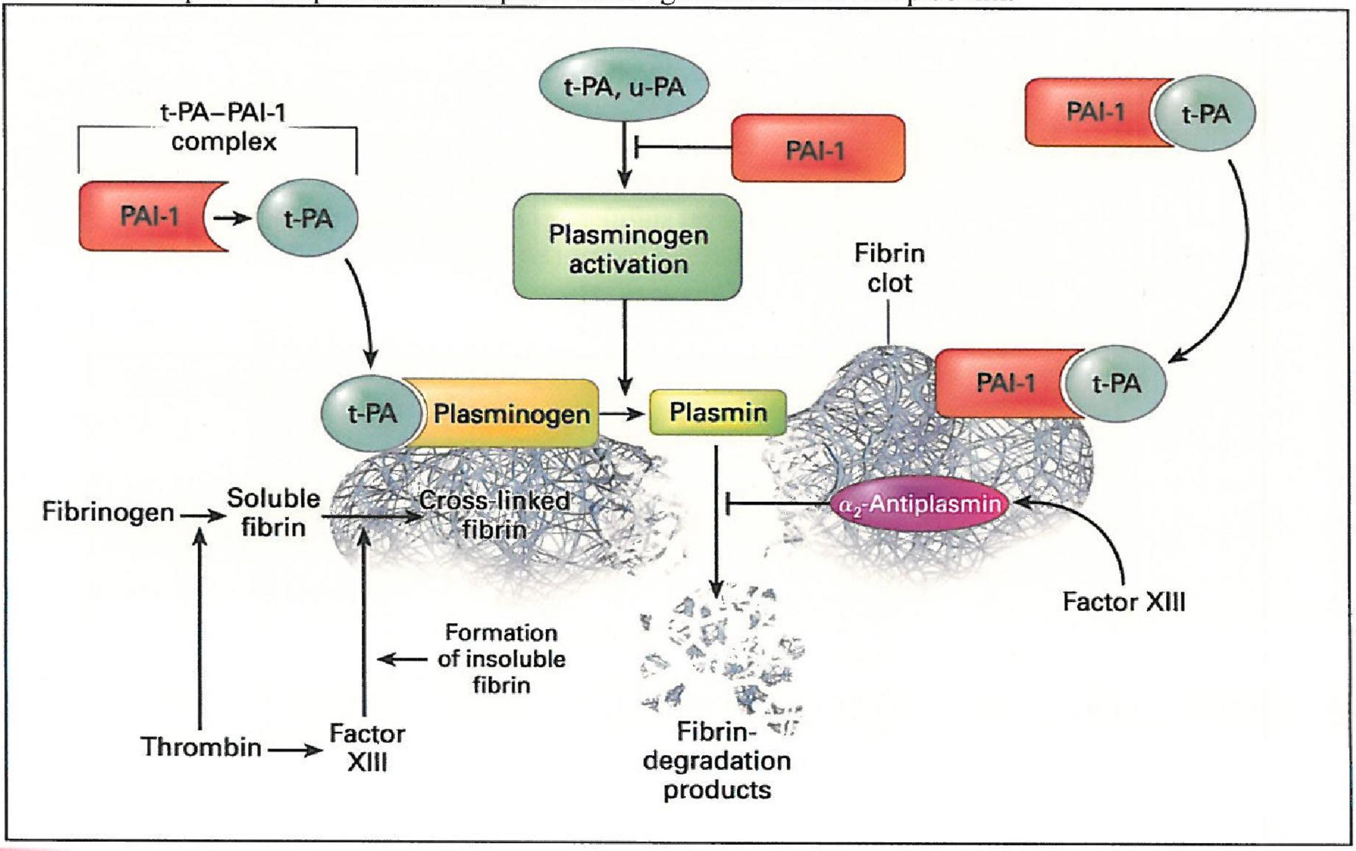
➢ *Finally*:-


Tissue factor
Surfaces (eg collagen)
VII
XIIa
XII
XIa
XI
IXa
IX
VIIIa
X
Xa
V
II (prothrombin)
IIa(Thrombin)
XIII
XIIIa
Fibrinogen
Fibrin
Stabilised Fibrin



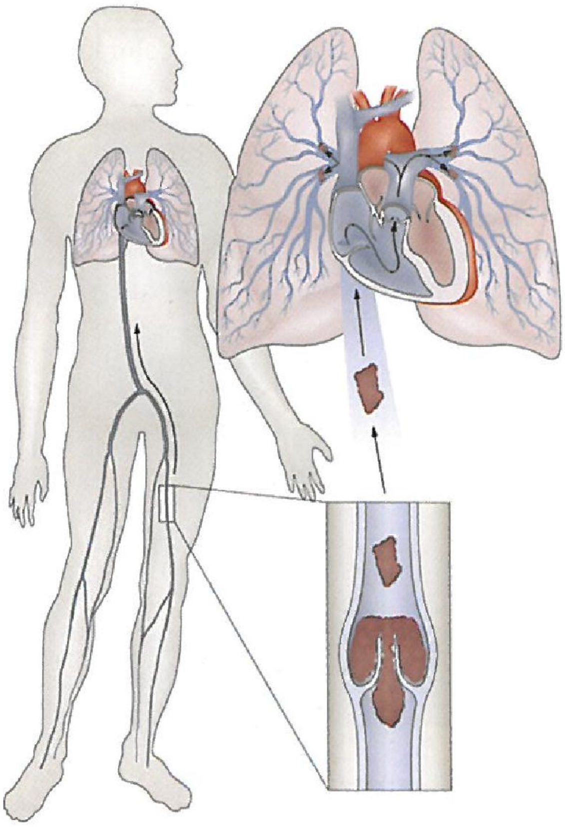
➢ Fibrinolysis:-

- *Fibrinolysis*; is a critical hemostatic process that regulates control of clot dissolution and hence wound repair, also plays key roles in inflammation, neoplastic and other biological processes.
- ***The major components of fibrinolysis*** are **plasminogen activators**, **plasminogen**, **plasmin**, **fibrinogen**, **fibrin**, **Factor XIII**, **alpha-2 antiplasmin** and **plasminogen activator inhibitor**.
- Tissue plasminogen activator (t-PA) and urokinase plasminogen activator (u-PA) circulate in plasma as a reversible complex with plasminogen activator inhibitor-1 (PAI-1)
- **t-PA** and **u-PA** are the agents that ***convert*** **plasminogen** to the **active plasmin** ⇨ **fibrinolysis**.
- **t-PA** and **u-PA** are themselves ***inhibited by*** **plasminogen activator inhibitor-1** and plasminogen **activator inhibitor-2** (**PAI-1** and **PAI-2**).
- Alpha 2-antiplasmin and alpha 2-macroglobulin inactivate plasmin.


t-PA–PAI-1 complex
PAI-1
t-PA
t-PA, u-PA
PAI-1
Plasminogen activation
PAI-1
t-PA
Fibrin clot
PAI-1
t-PA
t-PA
Plasminogen
Plasmin
Fibrinogen
Soluble fibrin
Cross-linked fibrin
α2-Antiplasmin
Factor XIII
Formation of insoluble fibrin
Thrombin
Factor XIII
Fibrin-degradation products

Venous Thromboembolism (VTE)

➢ Definition:-



- **Venous Thromboembolism** (VTE) is the formation of blood clots in the vein.
  - When a clot forms in a deep vein, usually in the leg, ***it is called***;

    Deep Vein Thrombosis (DVT).
  - If that clot breaks loose and travels to the lungs, ***it is called***;

    Pulmonary Embolism (PE).
  - ***Together***, DVT and PE are known as **VTE**.
- **Venous thromboembolism (VTE)**; is a disease that includes both deep vein thrombosis (DVT) and pulmonary embolism (PE).
- **Deep Vein Thrombosis (DVT)**; a blood clot that forms in a deep vein (usually in the leg).
- **Pulmonary Embolism (PE)**; a blood clot in the lungs.
  - PE occurs when a DVT breaks free from a vein wall, travels to the lungs and blocks some or all of the blood supply to the lungs. PE can often be fatal.

➢ Prevalence:-

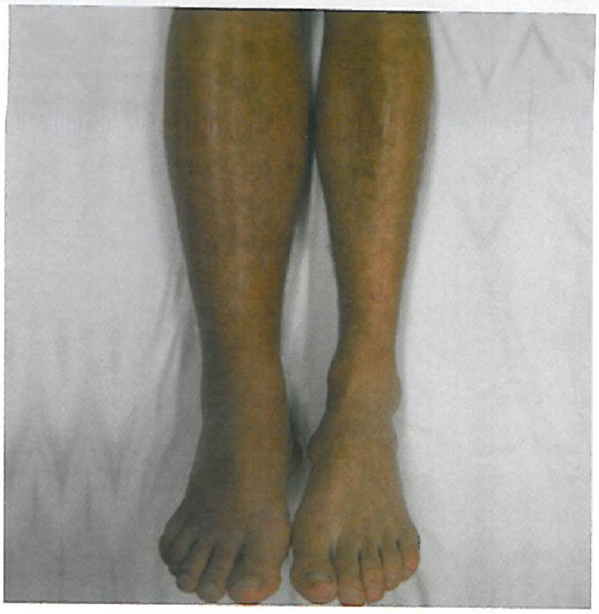
- **Venous thromboembolism** is the **third *most common* cardiovascular illness *after*** acute coronary syndrome and stroke.
- It is believed that there are approximately **1 million** cases in the **United States *each year***.
- Nearly **two thirds** of **all VTE events *result*** from **hospitalization** and approximately **300,000** of these patients ***die***.
- DVT and PE is low, and much lower than awareness of other diseases like heart attack, stroke, hypertension, breast cancer, prostate cancer and AIDS.

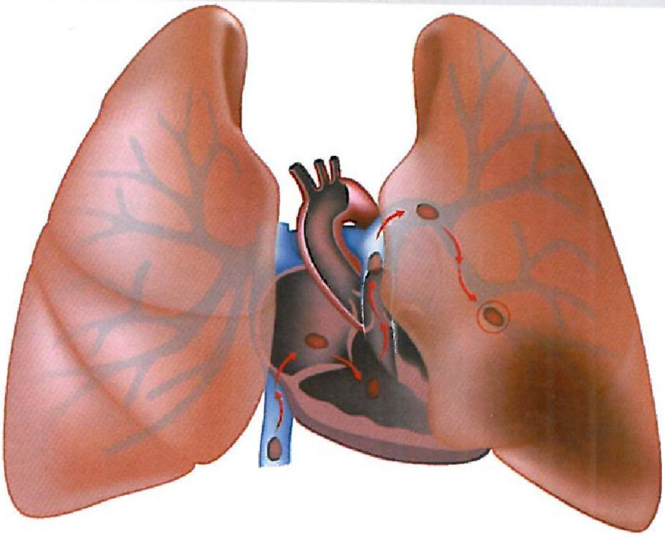
➢ Risk Factors:-

- VTE affects people of all ages, races and ethnicities and occurs in both men and women.
- Certain factors and situations can increase the risk of developing potentially deadly blood clots.
  - During surgery (especially hip, knee and cancer-related surgery).
  - Not moving for long periods of time (e.g. long-duration travel).
  - Age (> 60).
  - Family history of blood clots.
  - Cancer chemotherapy.
  - Estrogen-based medication (e.g., oral contraceptives).
  - Obesity.
  - Pregnancy or recent birth.
  - Smoking.
  - Alcohol consumption.

➢ Symptoms:-

Deep Vein Thrombosis (DVT)	Pulmonary Embolism (PE)
- Pain or tenderness, often starting in the calf.	- Unexplained shortness of breath.
- Swelling, including the ankle or foot.	- Rapid breathing.
- Redness or noticeable discoloration.	- Chest pain (may be worse upon deep breath).
- Warmth.	- Rapid heart rate.
	- Light headedness or passing out.





➢ Diagnosis:-

Deep Vein Thrombosis (DVT)	Pulmonary Embolism (PE)
1) ***Duplex ultrasound***; device generates sound waves show blood flow.	1) **Ultrasound**.
2) **D-dimer test** (blood test); almost all people who develop severe deep vein thrombosis have an elevated blood level of a clot-dissolving substance called D-dimer.	2) **D-dimer test**.
3) **Venography**; If the results of a D-dimer test and ultrasound scan cannot confirm a diagnosis of DVT, a venogram might be used. A dye (contrast agent) is injected into a large vein in the foot or ankle. An X-ray procedure creates an image of the veins in the legs and feet, to look for clots.	3) **Pulmonary Angiogram**; a flexible tube (catheter) is inserted into a large vein (usually in groin) and threaded through into the heart and on into the pulmonary arteries. A special dye is then injected into the catheter, and X-rays are taken as the dye travels along the arteries in the lungs.
4) **CT** or **MRI scans**. Both computerized tomography (CT) scan and magnetic resonance imaging (MRI) can provide visual images of the veins and may show a clot.	4) **Chest X-ray**; Although X-rays can't diagnose pulmonary embolism and may even appear normal when pulmonary embolism exists, they can rule out conditions that mimic the disease.
	5) **CT** or **MRI scans**.
	6) **Lung ventilation/perfusion scan** (**VQ scan**); a radioactive substance to show how well oxygen and blood are flowing to all areas of the lungs.

➢ Treatments:-

- *Medications*; **thrombolytics** and **anticoagulants** (*see next topics*).
- *Surgical and other procedures*; **clot removal** or **vein filter**.

Antithrombotic Drugs

- ***Antithrombotics Classification***:
  1) **Anticoagulants**; limit the ability of the blood to clot.
  2) **Thrombolytic *or* Fibrinolytic Drugs**; act to dissolve clots after they have formed.
  3) **Antiplatelet Drugs**; limit the migration or aggregation of platelets.

Anticoagulant Drugs

- ***Anticoagulants Classification (Mechanism)***:
  1) **Indirect Thrombin Inhibitors (Heparins).**
  2) **Direct Thrombin Inhibitors (DTIs).**
  3) **Direct Factor Xa Inhibitors.**
  4) **Vitamin K Antagonist (Coumarin Anticoagulants).**

Heparins (Unfractionated heparin & low-molecular weight heparin)

- **Heparin** [HEP-a-rin] (from Greek word 'hêpar' "liver") was discovered in 1916 by *McLean*, a second-year medical student, was working under the guidance of Howell investigating pro-coagulant preparations, when he isolated a fat-soluble phosphatide anticoagulant in canine liver tissue.
- **Heparin** is an **injectable rapidly acting anticoagulant** that is often ***used* acutely** to ***interfere*** with the **formation** of **thrombi**.
- **Heparins *also called***; **indirect thrombin inhibitors** because their anti-thrombotic effect is exerted by their interaction with a separate protein, antithrombin.
- ***Source***; Heparin occurs ***naturally*** as a macromolecule complexed with histamine in **mast cells**. It is ***extracted*** for commercial use from **porcine or cattle intestinal mucosa**.

Unfractionated Heparin (UFH)

Heparin (Calciparine®)

- **Unfractionated Heparin (UFH)**; is a ***mixture*** of varying chain size of **sulfated glycosaminoglycans *with*** a **wide range of molecular weights.**

Low Molecular Weight Heparins (LMWHs)

Enoxaparin (Clexane®)	**Dalteparin** (Fragmin®)	**Tinzaparin** (Innohep®)

- **Low Molecular Weight Heparins (LMWHs)** ***such as***; **Enoxaparin** [e-NOX-a-par-in], **Tinzaparin** [TIN-za-PAR-in] and **Dalteparin** [DAL-te-PAR-in] are **heterogeneous compounds** about ***one-third*** the **size** of unfractionated heparin, ***produced by*** enzymatic depolymerization of UFH.

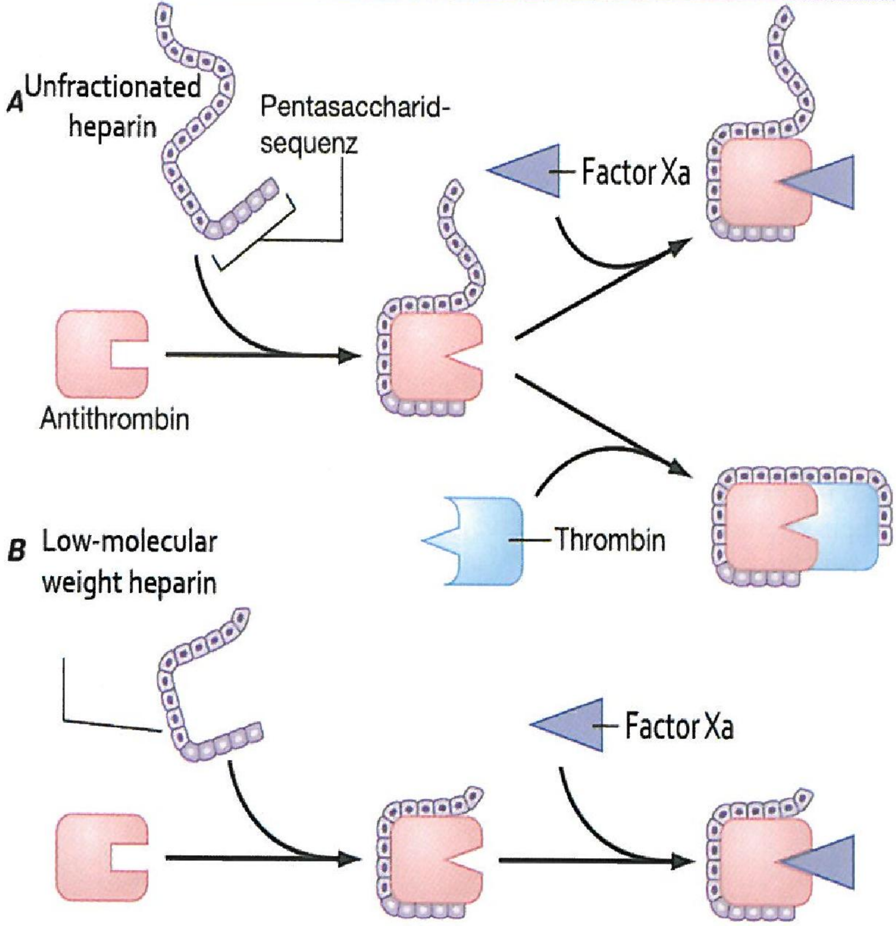
Pharmaco Kinetics

	Unfractionated Heparins (UFH)	Low-molecular weight heparins (LMWHs)
Routes	***Must be* SC or IV *only*** - The LMWHs are administered SC. - UFH is often initiated as an IV bolus followed by continuous infusion. - **Avoid IM**; ***cause***; irritation, erythema, pain, hematoma or ulceration.	
Mwt.	> 30000 Dalton	< 8000 Dalton
Bioavailability	Low	High
Dose	Loading dose, followed by continuous infusion (Unfixed dose)	Once or twice daily (Fixed dose)
Half-life	1.5 hours	3-12 hours
Price	Cheep	Expensive
Monitoring	Activated partial thromboplastin time (aPTT)	None
Factors Effected	Thrombin, IXa and Xa (less effect on Xa)	Xa

Pharmaco Kinetics

- **Anticoagulant effect *with*** unfractionated heparin occurs within minutes of IV administration or 1 to 2 hours after subcutaneous injection.
- **Activated partial thromboplastin time (aPTT)** is the standard test used to monitor the extent of anticoagulation with heparin.
- The maximum **anti–factor Xa activity *of*** the LMWHs occurs about 4 hours after subcutaneous injection.
- ***Not necessary*** to **monitor coagulation values *with* LMWHs *because*** the plasma levels and pharmacokinetics are more predictable, ***but*** in renally impaired, pregnant and obese patients monitoring of factor Xa levels is recommended with LMWHs.
- ***Dose*** of **LMWHs *should be* reduced** in patients with renal impairment.

Mechanism OF Action



- ***In the absence*** of **heparin, antithrombin III *interacts*** very slowly with **thrombin** and **factor Xa**.
- **UFH**; Heparin molecules ***bind*** to **antithrombin III (AT-III)** ⇨ ***conformational change*** occurs ⇨ ***activation*** of **AT-III** ⇨ ***inhibition*** of **thrombin** about 1000-fold ***and*** **factor Xa**.
- **LMWHs**; One molecules ***bind*** to with **AT-III** ⇨ ***inactivate*** **factor Xa**.
- A unique **pentasaccharide sequence** ***contained*** in **heparin** and **LMWHs *permits* their binding to antithrombin III**.

Therapeutic Uses

- Heparin and the LMWHs ***limit*** **the expansion of thrombi** by ***preventing*** **fibrin formation**.
- ***These agents are used for***;
  - ***Treatment of*** **acute venous thromboembolism** (**DVT** or **PE**).
  - ***Prophylaxis of*** **postoperative venous thrombosis *in patients* undergoing surgery and those with acute MI**.
  - ***Drug of choice for using in*** **pregnant women** (do not cross the placenta).

Dose

- ***Dose***;
  - **UFH**;
    - ***Initial bolus injection***; 80-100 units/kg, followed by; ***Continuous infusion***; 15-22 units/kg/h (*monitoring is needed*).
    - ***Prophylaxis***; 5000 units SC every 8–12 h (*monitoring is needed*).
  - **Enoxaparin**; SC 30 mg twice daily or 40 mg once daily, *alternatively*; 1 mg/kg SC every 12 hours or 1.5 mg/kg once a day.
  - **Dalteparin**; 200 units/kg once a day for venous disease or 120 units/kg every 12 hours for acute coronary syndrome.
  - **Tinzaparin**; 175 units/kg SC once daily.
- ***Monitoring of Heparin Effect***;
  - **Activated Partial Thromboplastin Time (aPTT)** is necessary in patients receiving UFH; ***reference range*** = 30-50 seconds.
  - LMWHs levels are not generally measured ***except*** in renal insufficiency, obesity (> 150 kg) and pregnancy.
  - LMWHs levels can be determined by **anti-Xa units**; ***therapeutic levels*** should be 0.5-1 unit/mL for twice-daily dosing, determined after 4 hours administration and 1.5 units/mL for once-daily dosing.

Side Effects

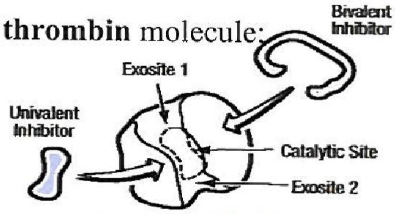
1) **Bleeding**;
   - ***Major*** **adverse effect of heparin**.
   - ***Monitoring*** is **required** to minimize bleeding.
   - ***Excessive bleeding*** may be **managed** by **discontinuing** the drug ***or*** by ***treating*** with **protamine sulfate**.
2) **Hypersensitivity Reaction**;
   - ***Such as***; chills, fever, urticaria, and anaphylactic shock, ***due to***; heparin is of animal origin.
   - Heparin and LMWHs are ***contraindicated*** in patients who have hypersensitivity to heparin.
3) **Thrombocytopenia**;
   - **Heparin-induced thrombocytopenia (HIT)** is a serious condition that occurs in 1-4% of individuals treated with UFH for a minimum of 7 days.
   - The risk of HIT may be higher in individuals treated with UFH of bovine origin compared with porcine heparin and is lower in those treated exclusively with LMWH.
   - HIT is caused by the formation of abnormal antibodies (immune-mediated) that activate platelets.
   - Morbidity and mortality in HIT are related to thrombotic events (venous thrombosis occurs most commonly).
   - Heparin therapy should be discontinued when patients develop HIT.
   - In cases of HIT, heparin can be replaced by another anticoagulant, such as **Argatroban**.
4) ***Other Side Effects***;
   - **Osteoporosis** has been observed in patients on long-term therapy.
   - **Hair loss** and **alopecia** have been reported.

Protamine Sulfate

- **Protamine** is a highly basic ***positively*** **charged** peptide that combines with ***negatively*** **charged heparin** as an ion pair to form a stable complex devoid of anticoagulant activity.
- For every **100 units of heparin** remaining in the patient, **1 mg of protamine sulfate** is given **IV infusion** (rate ***should not exceed*** 50 mg in any 10-minute period).
- Excess protamine must be avoided (it also has an anticoagulant effect).
- Neutralization of **LMWHs** by protamine is incomplete, limited experience suggests that 1 mg of protamine sulfate may be used to partially neutralize 1 mg of enoxaparin.

Direct Thrombin Inhibitors (DTIs)

- There are ***two types*** of DTIs, dependent on their **interaction with the thrombin** molecule;

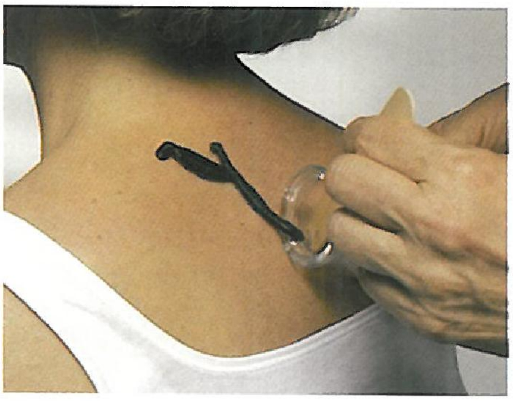


  - **Bivalent** DTIs bind both to the active site and exosite 1.
    - ***Includes***; **Hirudin**, **Bivalirudin**, **Lepirudin** and **Desirudin**.
  - **Univalent** DTIs bind only to the active site.
    - ***Includes***; **Argatroban**, **Ximelagatran** (withdrawn due to hepatotoxicity) and **Dabigatran**.

Parenteral Direct Thrombin Inhibitors

Bivalirudin (Angiomax®)	**Lepirudin** (Refludan®)	**Desirudin** (Iprivask®)

- In 1884 *John Berry Haycraft* described a substance found in the saliva of **leeches "*Hirudo medicinalis*"** that had anticoagulant effects. He named the substance '**Hirudin**'.
- **Hirudin** is a specific, ***direct thrombin inhibitor***.
- Leeches have been used in medicine for centuries and were first employed in ***Egypt*** about 2,500 years ago.



- ***Leech Therapy***;

  - Many people are now taking to leech therapy to treat hypertension, varicose veins, hemorrhoids, arthritis and skin problems.
  - ***Demi Moore*** (American actress) said she let leeches suck her blood as part of a therapy to look fresh and young it made headlines.
- **Direct Thrombin Inhibitors (DTIs)** have undergone rapid development since the 90's. With technological advances in genetic engineering the production of recombinant Hirudin was made possible which opened the door to this new group of drugs.
- **Bivalirudin** [bye-VAL-ih-ruh-din], **Lepirudin** [le-PEER-u-din] and **Desirudin** [deh-SIHR-uh-din] are parenteral direct thrombin inhibitor that are analogs of **Hirudin**.
- ***Mechanism***; Directly inhibits thrombin by binding ***both*** to **catalytic site** and **anion-binding exosite**.
- ***Pharmacokinetics***;
  - ***Like heparin***, it must be ***administered*** **parenterally** and is **monitored** by the **aPTT**.
  - **Bivalirudin**; elimination related to glomerular filtration rate.
  - **Lepirudin**; about 48% of the administered dose is excreted by the kidney.
  - **Desirudin**; metabolized and eliminated by the kidney.
  - ***So***; they are ***should be*** **used with great caution** in **patients with renal insufficiency** as ***no*** **antidote exists**.
- ***Uses***;
  - **Bivalirudin** also ***inhibits*** **platelet activation** and has been FDA-approved for use in **percutaneous coronary intervention (PCI)**.
    - **Dose**; initial: 0.75 mg/kg *IV bolus*, followed by *continuous infusion*: 1.75 mg/kg/hour over 4 hours, may be continued at 0.2 mg/kg/hour for up to 20 hours, patients should also receive aspirin 300-325 mg/day.
  - **Lepirudin** is approved by the FDA for use in **patients with thrombosis related to heparin-induced thrombocytopenia (HIT)**.
    - **Dose**; Initial: 0.4 mg/kg *IV slowly* (over 15 to 20 seconds) followed by 0.15 mg/kg/hr IV *continuous infusion* for 2 to 10 days or longer if clinically needed.
  - **Desirudin** is approved by the FDA for use for ***prophylaxis*** of **deep vein thrombosis**, ***which may lead to*** **pulmonary embolism**, ***in patients undergoing*** **elective hip replacement surgery**.
    - **Dose**; 15 mg SC every 12 hr; initiate 5-15 min before surgery (but after induction of regional block anesthesia) and continue for 9-12 days.
- ***Side effects***; ***Like the others***, **bleeding** is the major side effect of these agents.
  - Up to 40% of patients who receive long-term infusions of **Lepirudin** develop an **antibody**, which may develop **life-threatening anaphylactic reactions**.

Argatroban (Argatroban®)

- **Argatroban** [ar-GAT-roe-ban] is a synthetic parenteral direct thrombin inhibitor that is derived from l-arginine amino acids.
- ***Mechanism***; It is a **direct thrombin inhibitor** that ***reversibly*** **binds to the thrombin active site.** It does not require the co-factor antithrombin III for antithrombotic activity.
- ***Pharmacokinetics***; It is ***metabolized*** in the **liver** and has a ***half-life*** of about **39-51 minute.**
- ***Uses***;
  - ***Prophylaxis*** or ***treatment*** of **thrombosis** in **patients with heparin-induced thrombocytopenia (HIT).**
  - ***During*** **percutaneous coronary interventions (PCI)** in **patients who have HIT** or **are at risk for developing it.**
- ***Dose***; ***Before*** administering Argatroban; ***discontinue*** **heparin therapy** and ***obtain*** a **baseline aPTT**. The recommended ***initial dose*** for adult patients without hepatic impairment is **2 mcg/kg/min** as a continuous infusion, ***monitoring is needed*** (aPTT).
- ***Side effects***; As with other anticoagulants, the major side effect is bleeding.
- ***Contraindication***; Patients with hepatic impairment.

Oral Direct Thrombin Inhibitors

- ***Advantages*** of **oral direct thrombin inhibitors**;
  - Predictable pharmacokinetics and bioavailability, which allow for fixed dosing.
  - Predictable anticoagulant response.
  - Routine coagulation monitoring unnecessary.

Dabigatran Etexilate (Pradaxa®)

- **Dabigatran Etexilate** [da-bi-GAT-ran e-TEX-i-late] is the direct thrombin inhibitor approved by the FDA in 2010.
- ***Mechanism***; is a direct thrombin inhibitor bind only to the active site.
- ***Pharmacokinetics***; **Dabigatran Etexilate** is the prodrug of the active moiety **Dabigatran.**
  - **Oral bioavailability** is 3-7%.
  - * **Oral bioavailability** ***may increase*** by up to **75%** when pellets are ***taken out*** of the **hydroxypropylmethylcellulose (HPMC) capsule**. Therefore, capsules ***should not*** be opened and pellets taken alone.
  - The **half-life** of the drug is 12-17 hours.
  - **Renal impairment** results in ***prolonged drug clearance*** and may **require dose adjustment** (***should be*** **avoided** in patients with **severe renal impairment**).
  - The drug is a substrate for the P-glycoprotein efflux pump; ***however***, P-glycoprotein inhibitors or inducers ***do not have*** a **significant effect** on drug clearance.
- ***Uses***;
  - ***Prevention*** **of stroke in non-valvular atrial fibrillation.**
  - ***Prevention*** **of venous thromboembolism (DVT and PE)** ***in patients who have undergone*** **hip** ***or*** **knee replacement surgery.**
- ***Dose***;
  - For patients with creatinine clearance (CrCl) **>30 mL/min**; **150 mg** taken orally, ***twice daily.***
  - For patients with severe renal impairment (CrCl **15-30 mL/min**); **75 mg** ***twice daily.***
  - ***No*** **monitoring** is required.
- ***Side effects***; The ***primary*** **toxicity** is **bleeding**, ***GI adverse effects*** are common with this drug and may include **dyspepsia, abdominal pain, esophagitis,** and **GI bleeding**.
- ***Drug interactions***; **Ketoconazole, Amiodarone, Quinidine,** and **Clopidogrel** ***increases drug effect.***
- ***Dabigatran antidote***; **Idarucizumab** (Praxbind®) is a monoclonal antibody and the ***first*** **reversal agent** for the **Dabigatran** has been approved by the FDA in October 16, 2015.

Direct Factor Xa Inhibitors

Parenteral Direct Factor Xa Inhibitors

Fondaparinux (Arixtra®)

- **Fondaparinux** [fawn-da-PEAR-eh-nux] is a ***pentasaccharide anticoagulant*** that is synthetically derived, is a chemically related to ***low molecular weight heparins*** (***LMWHs***).
- ***Mechanism***; Act by selective inhibition of factor Xa only, by selective binding to antithrombin III, it is potentiates (300- to 1000-fold) the innate neutralization of factor Xa by antithrombin III.
- ***Pharmacokinetics***;
  - SC administration.
  - ***Long*** half-life; 15 hours (once-daily).
  - ***Elimination***; in the urine as unchanged drug elimination half-life 17-21 hours.
- ***Uses***; ***Treatment*** or ***prophylaxis*** of **venous thromboembolism** (**DVT** and **PE**).
- ***Dose***;
  - A) ***Treatments***;
    - Under 50 kg: 5 mg subcutaneously once a day.
    - 50 to 100 kg: 7.5 mg subcutaneously once a day.
    - Over 100 kg: 10 mg subcutaneously once a day.
  - B) ***Prophylaxis***;
    - 2.5 mg SC once a day for 5 to 9 days.
- ***Side effects***; Major side effect is **bleeding** (***no antidote***).
- ***Contraindication***; Patients with **severe renal impairment** (CrCl less than 30 mL/min).
- ***FDA warning***; **Fondaparinux** ***should not be*** **used in the setting of lumbar puncture** or **spinal cord surgery,** ***Due to*** **risk of epidural or spinal hematomas.**

Oral Direct Factor Xa Inhibitors

Rivaroxaban (Xarelto®)

- **Rivaroxaban** [RIV-a-ROX-a-ban] is the first oral factor Xa inhibitor approved by the FDA in 2011.
- ***Mechanism***; Selectively blocks the active site of factor Xa.
- ***Pharmacokinetics***;
  - ***Bioavailability***;
    - 10 mg dose; 80-100% and is not affected by food.
    - 20 mg dose; 66% in the fasted state, with food ↑ the bioavailability.
  - ***Metabolism***; mainly by the CYP 3A4/5 and CYP 2J2 to inactive metabolites.
  - ***Elimination***; 51% of dose was recovered as metabolites in urine.
- ***Uses***;
  - ***Prevention*** **of stroke in non-valvular atrial fibrillation.**
    - ***Dose***; 20 mg orally once a day.
  - ***Prophylaxis*** **of deep vein thrombosis** (**DVT**) which may lead to **pulmonary embolism** (**PE**) ***in patients undergoing*** **knee** or **hip replacement surgery**.
    - ***Dose***;
      - ***In*** **DVT or PE**; ***Initial***: 15 mg orally twice a day for first 21 days of therapy. ***Maintenance***: 20 mg orally once a day for the remaining duration of treatment.
      - ***In*** **DVT or PE recurrence**; 20 mg orally once a day.
      - ***In*** **DVT prophylaxis after hip or knee replacement surgery**;
        - ***Initial***: 10 mg orally once a day starting 6 to 10 hours after surgery.
        - ***Duration of therapy***: Hip: 35 days - Knee: 12 days.
- ***Side effects***; Major side effect is **bleeding** (***no antidote***).
- ***Contraindication***; Patients with **severe renal impairment** (CrCl less than 30 mL/min in DVT and CrCl less than 15 mL/min in non-valvular atrial fibrillation).

Apixaban (Eliquis®)

- **Apixaban** [a-PIX-a-ban] is an oral selective inhibitor of factor Xa.
- ***Pharmacokinetics***; ***Metabolism***; Mainly by the CYP3A4. ***Elimination***; 27% is excreted renally.
- ***Uses***; - ***Prevention of* stroke in non-valvular atrial fibrillation.**
  - ***Dose***; 5 mg taken orally twice daily.
  - ***Prophylaxis of* deep vein thrombosis (DVT)** which may lead to **pulmonary embolism (PE)** ***in patients undergoing* knee or hip replacement surgery.**
    - ***Dose***; - ***In* DVT or PE**; 10 mg orally twice daily for the first 7 days. After 7 days, the recommended dose is 5 mg taken orally twice daily.
      - ***In* DVT or PE recurrence**; 2.5 mg taken orally twice daily after at least 6 months of treatment for DVT or PE.
      - ***In* DVT prophylaxis after hip or knee replacement surgery**; 2.5 mg taken orally twice daily, taken 12-24h after surgery. - ***Duration of therapy***: Hip: 35 days - Knee: 12 days.
- ***Side effects***; Major side effect is **bleeding (NOW**; ***antidote*** is ***available***).
- ***FDA warning***; **Apixaban** ***should not be*** **used in the setting of lumbar puncture** or **spinal cord surgery**, ***Due to*** **risk of epidural or spinal hematomas.**
  - ***Premature*** **discontinuation** of **Apixaban**, ***increases*** the **risk of thrombotic events.**

Edoxaban (Savaysa®) (Lixiana®)

- **Edoxaban** is an ***oral*** **direct factor Xa inhibitor**. It was ***developed*** by and ***approved*** in **2011** in **Japan** for ***prevention*** of **venous thromboembolisms (VTE)** *following* **lower-limb orthopedic surgery.**
- It was also ***approved*** by the **FDA** in **January 2015** for **venous thromboembolism** and **non-valvular atrial fibrillation.**

Factor Xa Inhibitor Antidote

- **Andexanet alfa** (AndexXa®) is an ***antidote*** for **factor Xa inhibitors** (**Rivaroxaban** and **Apixaban**). It was ***approved*** by the **FDA** in **May 2018**.

Vitamin K Antagonists (Coumarin Anticoagulants)

- **Vitamin K antagonists** were the ***only class*** of **oral anticoagulants available** to clinicians ***for decades***.
- ***However***, after FDA approval of **new oral anticoagulants** ***or*** **novel oral anticoagulants (NOACs)** including **Dabigatran**, **Rivaroxaban**, and **Apixaban** have been shown to be as ***better than*** the **vitamin K antagonists** ***with less*** **serious side effects.**

Warfarin (Coumadin®) (Marevan®)

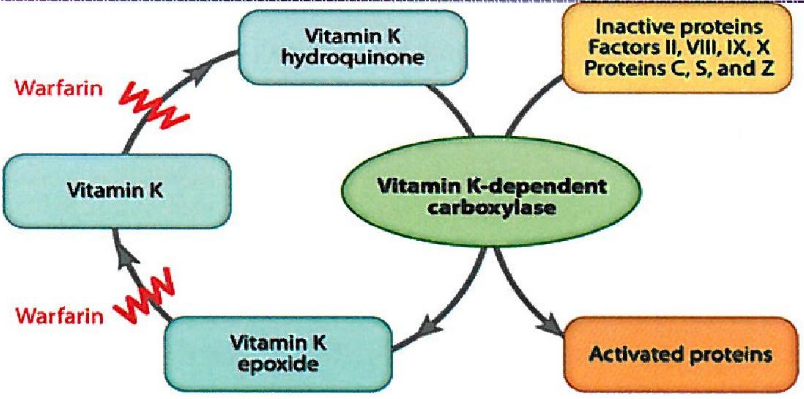
KILL-RATS!
STOP
THIS ROBBER
WARFARIN

- **Warfarin** [WAR-far-in] is a synthetic ***derivative*** of **Dicumarol** (natural chemical substance of combined plant and fungal origin). **Dicumarol** is derived from **Coumarin**, a sweet-smelling found naturally in **Sweet clover** and **Tonka beans** (also known as "cumaru" from which coumarin's name derives).
- In the early 1920s, **Coumarin anticoagulants** began with the discovery of an anticoagulant substance formed in spoiled sweet clover silage which caused ***hemorrhagic disease*** in **cattle**.
- The name '**Warfarin**' stems from its discovery at the University of Wisconsin, incorporating the acronym for the organization that funded the key research, "**WARF**" for the **W**isconsin **A**lumni **R**esearch **F**oundation and the ending "**-arin**", indicating its link with Coumarin.
- Warfarin was first registered for use as a rodenticide in the US in 1948, and was immediately popular.
- After an incident in 1951, where a US Army inductee unsuccessfully attempted suicide with multiple doses of warfarin in rodenticide and recovered fully after presenting to a hospital, and being treated with vitamin K (specific antidote), studies began in the use of warfarin as a therapeutic anticoagulant.
- In 1954 **Warfarin** (under the brand name Coumadin®) was approved for medical use in humans.
- ***Now*** **Warfarin** is one of the ***most commonly*** **prescribed drugs**, used by ***approximately*** **1.5 million individuals.**
- **Phenindione** (Dindevan®) is another synthetic ***derivative*** of **Dicumarol**, has actions similar to warfarin, but it is now rarely employed because of its higher incidence of severe adverse effects.

Pharmaco Kinetics

- ***Chemistry***; Warfarin used clinically is a racemic mixture composed of equal amounts of two enantiomorphs. The **levorotatory S-warfarin** is **4 times *more potent than*** the **dextrorotatory R-warfarin**.
- ***Absorption***;
  - ***Rapidly* absorbed** after oral administration.
  - ***Oral bioavailability*** = 100%.
- ***Distribution***;
  - Warfarin readily crosses the placental barrier.
  - ***Over*** 99% of racemic warfarin is bound to plasma albumin.
- ***Metabolism***;
  - Warfarin is metabolized by the CYP450 system.
- ***Excretion***;
  - ***Half-life***; Mean half-life is approximately 40 hours.
  - The inactive metabolites are excreted in urine and feces.
- Drugs that affect warfarin binding to plasma proteins or warfarin metabolism can lead to numerous drug interactions that may potentiate or attenuate its anticoagulant effect.

Mechanism OF Action


Vitamin K hydroquinone
Inactive proteins Factors II, VIII, IX, X Proteins C, S, and Z
Warfarin
Vitamin K
Vitamin K-dependent carboxylase
Warfarin
Vitamin K epoxide
Activated proteins

- **Warfarin *inhibits* vitamin K epoxide reductase enzyme**, resulting in depletion of the reduced form of vitamin K.
- **Vitamin K** is a ***cofactor*** for the **carboxylation of glutamate residues** on the N-terminal regions of vitamin K-dependent proteins, this limits the gamma-carboxylation and subsequent activation of the vitamin K-dependent coagulant proteins.
- **The synthesis** of **vitamin K-dependent coagulation factors** II, VII, IX, and X and anticoagulant proteins C and S is ***inhibited***.
- ***Depression*** of **vitamin K-dependent coagulation factors** (factors II, VII, and X) results in ***decreased* prothrombin levels** and a ***decrease*** in the amount of **thrombin** generated and bound to fibrin.

Actions

- **Production of clotting factors** are ***diminished activity*** (10-40% of normal) by warfarin treatment. ***Unlike* heparin**, the anticoagulant effects of warfarin are not observed ***immediately after drug administration***;
  - ***Peak anticoagulant effect*** may be delayed **72-96 hours** (the time required to deplete the pool of circulating clotting factors).
  - ***Treatment initiated*** with **UFH** or **LMWH** for the **first 5-7** days, with an overlap with **Warfarin**. Once therapeutic effects of warfarin have been established, therapy with warfarin is continued for a minimum of 3-6 months.
- The ***duration of action*** of a single dose of racemic warfarin is **2-5 days**.
- The **anticoagulant effects of warfarin** can be ***overcome*** by the administration of **vitamin K**, takes approximately 24 hours (the time necessary for degradation of already synthesized clotting factors).

Therapeutic Uses

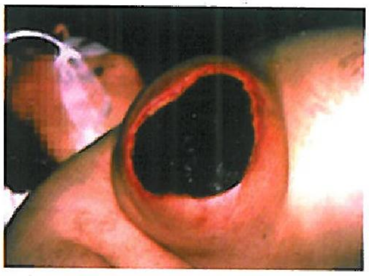
- ***Prophylaxis*** and ***treatment*** of **deep vein thrombosis (DVT)** and its extension, **pulmonary embolism (PE)**.
- ***Prophylaxis*** and ***treatment*** of **thromboembolic complications associated with atrial fibrillation (AF) *and/or* cardiac valve replacement**.
- ***Reduction*** in the **risk of death**, ***recurrent*** **myocardial infarction (MI) *and* thromboembolic events** such as **stroke**.
- **Protein C and S deficiency symptoms** (is an inherited disorder causes abnormal blood clotting).
- **Antiphospholipid syndrome** (is an autoimmune, hypercoagulable state caused by antiphospholipid antibodies).

Dose

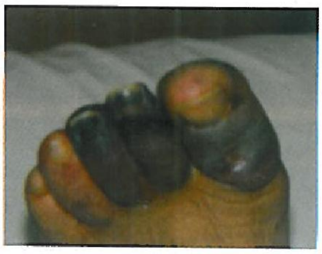
- The dosage and administration of warfarin must be individualized for each patient according to the patient's INR response to the drug.
- **International Normalized Ratio (INR)**; is the prothrombin time ratio (patient prothrombin time/mean of normal prothrombin time for lab).
- Adjust the warfarin dose to maintain a target INR of 2.5 (INR range, 2.0-3.0) for all treatment durations.
- ***Initial dose***: 2-5 mg orally or IV once a day for 1-2 days, then adjust dose according to results of the INR or prothrombin time (PT).
- ***Maintenance dose***: 2-10 mg orally or IV once a day.

Side Effects

1) **Hemorrhage**;
   - ***The major side effect*** is **hemorrhage** and the agent has a **black box warning *for* bleeding risk**.
   - ***Therefore***, it is important **monitoring**.
   - ***Minor bleeding*** may be treated by withdrawal of the drug or administration of oral vitamin K (**warfarin antidote**), ***but*** **severe bleeding** may require high doses of vitamin K given IV.
2) **Warfarin Necrosis**;
   - ***Rare complications*** of warfarin therapy, predominantly 4 times ***more common*** in **obese women**.
   - **Typically occurs *within*** 10 days of the initiation of therapy, ***but*** has occurred after several months or several years of therapy.

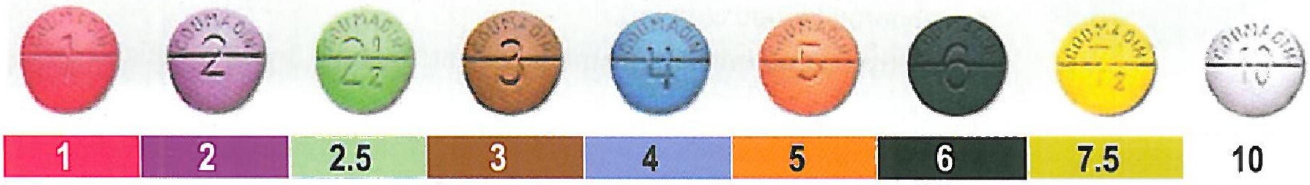


   - 80% occur in areas with **abundant adipose *such as*** the thighs, breasts, abdomen, buttocks, and the extremities.
   - Usually painful, abrupt in onset, erythematous, purpuric and sharply demarcated.
   - ***Mechanism*** of warfarin-induced skin necrosis involves an imbalance between proteins C or S and vitamin K-dependent clotting factors.
3) **Osteoporosis**;
   - ***Due to*** reduced intake of vitamin K, which is necessary for bone.
4) **Purple Toe Syndrome**;
   - ***Rare complication***.
   - This condition is result from small deposits of cholesterol breaking loose and causing embolisms in blood vessels in feet, causes a blueish purple colour and may be painful.



- **Warfarin** is **teratogenic** and ***should never be*** **used during pregnancy**.
- ***If anticoagulant therapy is needed during pregnancy***, **Heparin** or **LMWH** may be administered.

- ***Color-Coded for Safety***; Generic warfarin tablets may come in different shapes, but each strength comes in just one color.
  - ***For example***, 5 mg tablet; peach/light orange color.



- **Warfarin** has **numerous drug interactions** that may ***potentiate*** or ***attenuate*** its **anticoagulant effect**.
- The list of interacting drugs is extensive.
- ***A summary of some of the important interactions***;

Increased Prothrombin Time		Decreased Prothrombin Time	
Pharmacokinetic	**Pharmacodynamic**	**Pharmacokinetic**	**Pharmacodynamic**
Amiodarone	**Drugs**	Barbiturates	**Drugs**
Cimetidine	Aspirin	Cholestyramine	Diuretics
Disulfiram	Cephalosporins (third-generation)	Rifampin	Vitamin K
Metronidazole	Heparin		
Fluconazole	**Body factors**		**Body factors**
Phenylbutazone	Hepatic disease		Hereditary resistance
Sulfinpyrazone	Hyperthyroidism		Hypothyroidism
Trimethoprim-Sulfamethoxazole			

Drug Interactions

- **Metronidazole**, **Fluconazole** and **Trimethoprim-Sulfamethoxazole** also stereo selectively ***inhibit*** **metabolism** ***of*** **S-warfarin**.
- **Amiodarone**, **Disulfiram** and **Cimetidine** ***inhibit*** **metabolism** of **both** enantiomorphs of warfarin.
- **Aspirin** ***augment*** warfarin's effects by its effect on **platelet** function.
- **Hepatic disease** and **hyperthyroidism** ***augment*** warfarin's effects by increasing the **turnover rate** of clotting factors.
- **Third-generation cephalosporins** ***kill*** the **bacteria** in the intestinal tract that produce vitamin K.
- **Barbiturates** and **Rifampin** cause a marked decrease of the anticoagulant effect by ***induction*** of the **hepatic enzymes** that transform racemic warfarin.
- **Cholestyramine** ***binds*** warfarin in the intestine and ***reduces*** **its absorption** and bioavailability.
- ***Diuretics***; **Chlorthalidone** and **Spironolactone** (clotting factor **concentration**).
- **Vitamin K**; ***increased*** **synthesis** of clotting factors.
- **Hereditary resistance**; ***mutation*** of vitamin K reactivation cycle molecules.
- **Hypothyroidism**; ***decreased*** **turnover rate** of clotting factors.

Food Interactions

- **Food** (or **drink**) **and supplements** that ***may*** interact with warfarin includes:
  - **Vitamin A** or **E** and **Glucosamine**, **Ginseng**, **Ginkgo biloba**, **Ginger**, **Coenzyme Q10** and **Bilberry**.
  - **Alcohol**, **cranberries/cranberry juice** and **Green tea**.
  - **Chickpeas** and **animal liver**.

Fibrinolytic Drugs

- **Fibrinolytic drugs** (**Thrombolytic drug**) rapidly lyse thrombi (dissolve blood clots) by catalyzing the formation of plasmin (serine protease) from its precursor plasminogen.
- The ***major side effects*** of **these drugs** are bleeding.
- **These drugs** are ***contraindicated*** in **pregnancy** and in ***patients with*** healing wounds, a history of cerebrovascular accident, brain tumor, head trauma, intracranial bleeding and metastatic cancer.

Streptokinase (SK) (Kabikinase®)

- **Streptokinase** [strep-toe-KYE-nase] **is a protein** synthesized by ***streptococci.***
- ***Mechanism***; **Streptokinase** combines with the pro-activator plasminogen to form ***enzyme complex***. This enzymatic complex catalyzes the ***conversion*** of **inactive plasminogen *to* active plasmin**.
- ***Uses***; **acute MI**, **DVT** and **PE**.
- ***Dose***; IV infusion of a loading dose of 250,000 units, followed by 100,000 units/h for 24-72 hours.
- **Streptokinase** has ***high*** **antigenicity**, ***so*** **patients** with ***anti-streptococcal antibodies*** can develop **fever**, **allergic reactions** and **therapeutic resistance**.
- **Streptokinase** is ***rarely*** **used** and is no longer available in many markets.

Urokinase (Angikinase®)

- **Urokinase** [URE-oh-KYE-nase] ***also called*** **urokinase-type plasminogen activator** (**uPA**), it is produced ***naturally*** in the body by the kidneys.
- **Therapeutic urokinase** is ***isolated*** from **cultures of human kidney cells** and has ***low*** **antigenicity**.
- ***Mechanism***; directly cleaves the arginine–valine bond of plasminogen to yield active plasmin.
- ***Uses***; **PE**, **DVT**, **acute MI**, **coronary artery thrombosis** and **arterial thrombosis**.
- ***Dose***; loading; 300,000 units over 10 min. and a maintenance; 300,000 units/h for 12 hours.

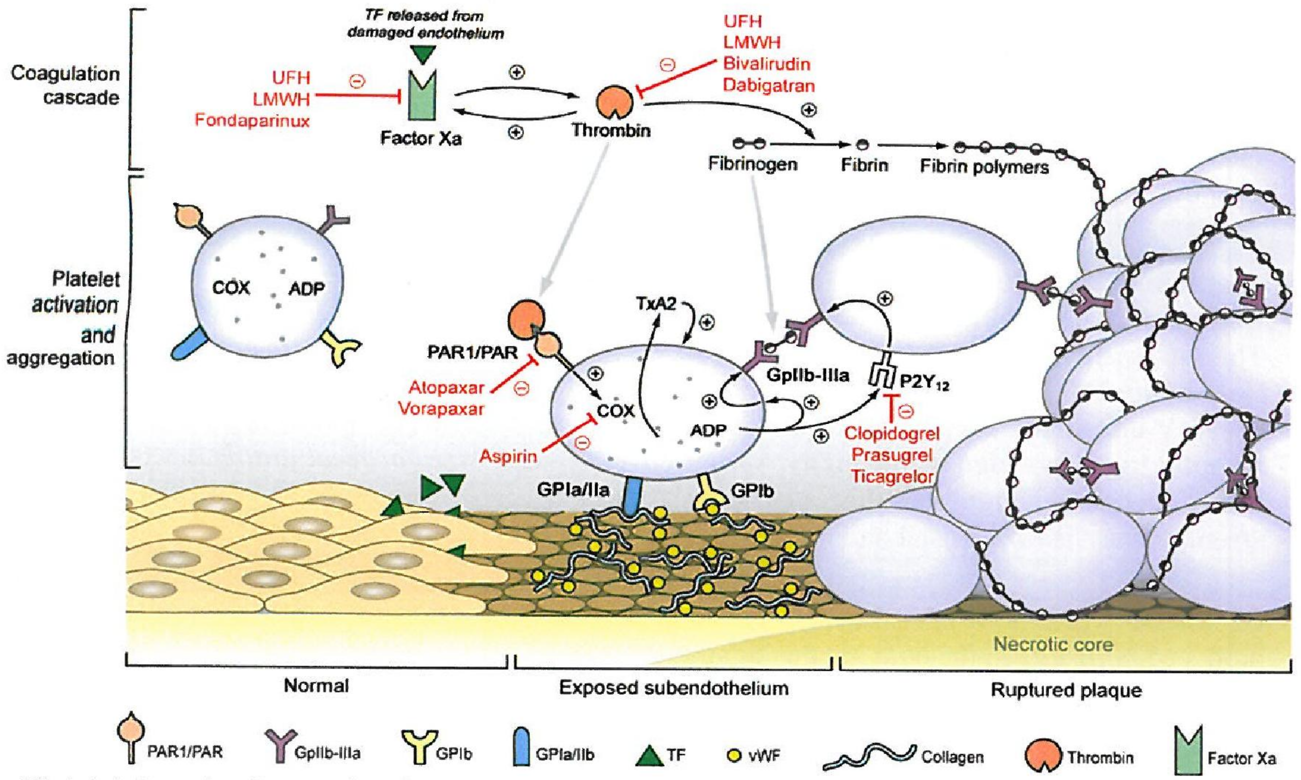
Anistreplase (Eminase®)

- **Anistreplase** [uh-NISS-truh-place] is ***also known as*** **anisoylated plasminogen streptokinase activator complex** (**APSAC**).
- ***Mechanism***; ***It is consists of*** a **complex *of* purified human plasminogen *and* bacterial streptokinase** that has been acylated to protect the enzyme's active site. ***When the drug is administered***, the acyl group gets hydrolyzed, thereby freeing the activator complex. It converts plasminogen to plasmin.
- ***Uses***; **acute MI**, now this drug is discontinued in the USA.
- ***Dose***; Single IV injection of 30 units over 2 to 5 min.

Alteplase (Cathflo® Activase®) | Reteplase (Retavase®) | Tenecteplase (TNKase®)

- **Plasminogen** can also be ***activated*** endogenously by **tissue plasminogen activators** (**t-PAs**).
- Human t-PA is manufactured as **Alteplase** [AL-teh-place] (by recombinant DNA technology), **Reteplase** [RE-teh-place] (by recombinant DNA technology) and **Tenecteplase** [ten-EK-te-place] is another recombinant tPA with a longer half-life and greater binding affinity for fibrin.
- ***Uses***;
  - **Alteplase**; **Treatment of acute MI**, **massive PE** and **acute ischemic stroke**.
    - ***Dose***; IV infusion (due to very short half-life; 5-30 minutes); 60 mg over the first hour and then 40 mg at a rate of 20 mg/h.
  - **Reteplase**; **Treatment of acute MI** (***off-label used*** in **DVT** and **massive PE**).
    - ***Dose***; Double IV bolus (moderate half-life) injections of 10 units (10+10) each, separated by 30 minutes.
  - **Tenecteplase**; **Treatment of acute MI**.
    - ***Dose***; Single IV bolus (long half-life) of 0.5 mg/kg.
- ***N.B***; **Alteplase** may cause angioedema, and there may be an increased risk of this effect when combined with angiotensin-converting enzyme (ACE) inhibitors.

Antiplatelet Drugs

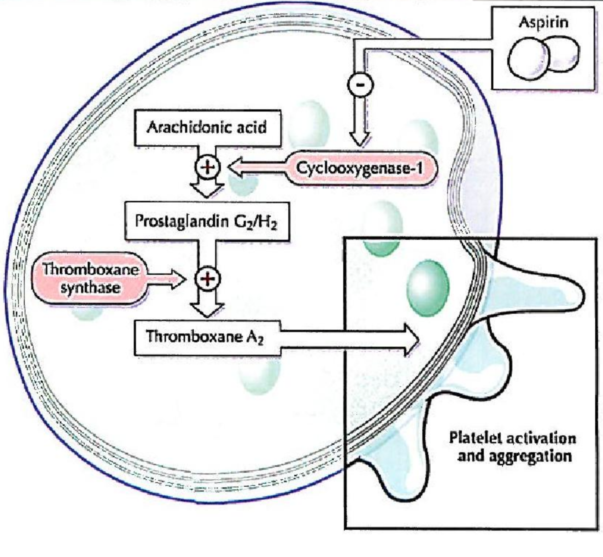

Coagulation cascade
TF released from damaged endothelium
UFH
LMWH
Fondaparinux
Factor Xa
Thrombin
UFH
LMWH
Bivalirudin
Dabigatran
Fibrinogen
Fibrin
Fibrin polymers
Platelet activation and aggregation
COX
ADP
TxA2
PAR1/PAR
Atopaxar
Vorapaxar
Aspirin
GpIIb-IIIa
P2Y12
Clopidogrel
Prasugrel
Ticagrelor
GPIa/IIa
GPIb
Necrotic core
Normal
Exposed subendothelium
Ruptured plaque
PAR1/PAR
GpIIb-IIIa
GPIb
GPIa/IIb
TF
vWF
Collagen
Thrombin
Factor Xa

- **Platelet function** is ***regulated by*** **three categories of substances**;
  1) The ***first*** group consists of agents generated ***outside*** the platelet that interact with platelet ***membrane receptors*** e.g. catecholamines, collagen, thrombin and prostacyclin.
  2) The ***second*** category contains agents generated ***within*** the platelet that interact with ***membrane receptors*** e.g. ADP, prostaglandin D_2, prostaglandin E_2 and serotonin.
  3) The ***third*** group comprises agents generated ***within*** the platelet that act ***within*** the platelet e.g. prostaglandin endoperoxides and thromboxane A_2, cAMP and cGMP and calcium ion.
- From this list of agents, several targets for platelet inhibitory drugs have been identified:
  1) ***Inhibit*** **Prostaglandin Synthesis** (**Aspirin**).
  2) ***Inhibit*** **ADP-induced Platelet Aggregation** (**Clopidogrel**, **Prasugrel** and **Ticlopidne**).
  3) ***Block*** **Glycoprotein IIb/IIIa Receptors** (**Abciximab**, **Tirofiban** and **Eptifibatide**).
  4) **Protease-Activated Receptor-1 (PAR-1)** ***Antagonists*** (**Vorapaxar** and **Atopaxar**).
  5) ***Other*** **Antiplatelet Drugs** (**Dipyridamole** and **Cilostazol**).

Thromboxane A_2 Inhibitor

Aspirin (Aspocid®)

- **Aspirin** [AS-pir-in] inhibits the synthesis of thromboxane A_2 by ***irreversible*** acetylation of cyclooxygenase (COX) enzyme.
- ***Other*** non-steroidal anti-inflammatory drugs also inhibit COX ***but*** have a ***shorter duration*** of inhibitory action ***because*** they cannot acetylate cyclooxygenase; that is their action is ***reversible***.
- **Aspirin inhibit platelet function *within* 60 min.**
- **Aspirin** is ***used*** in the ***prophylactic treatment*** **of transient cerebral ischemia and thromboembolic stroke**, and ***reduce*** **the incidence of recurrent MI.**
- The ***recommended dose***; ranges from **75-325 mg/d.**
- ***Side effects***; GI disturbances, ↑ bleeding time and may cause bronchospasm in susceptible patients.


Aspirin
Arachidonic acid
Cyclooxygenase-1
Prostaglandin G2/H2
Thromboxane synthase
Thromboxane A2
Platelet activation and aggregation

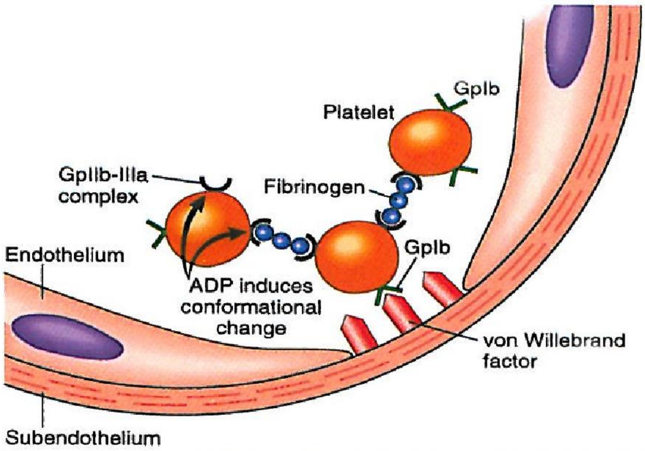
P_2Y_{12} Receptor Inhibitors

Clopidogrel (Plavix®) | **Ticlopidine** (Ticlid®) | **Prasugrel** (Effient®) | **Ticagrelor** (Brilinta®)

- **Clopidogrel** [kloh-PID-oh-grel], **Ticlopidine** [ti-KLOE-pi-deen], **Prasugrel** [PRA-soo-grel] and **Ticagrelor** [tye-KA-grel-or] are **$P2Y_{12}$ receptor inhibitors** that ***reduce*** **platelet aggregation** by ***inhibiting*** the **ADP pathway**.
- **Clopidogrel** (Plavix®) was the second best-selling drug in the world. In 2010, it grossed over US$9 billion in global sales.

Mechanism OF Action

- Acts by ***inhibit*** the **binding of ADP to its receptors ($P2Y_{12}$ receptor)** on platelets ⇨ ***inhibit*** the activation of **GP IIb/IIIa receptors** required for platelets to bind to fibrinogen and to each other.



- **Ticagrelor** binds to the $P2Y_{12}$ receptor ***reversible***.
- The **other agents** bind ***irreversibly***.
- *Max. inhibition of platelet aggregation;*
- **Clopidogrel**; 3-5 d.
- **Ticlopidine**; 3-4 d.
- **Prasugrel**; 2-4 h.
- **Ticagrelor**; 1-3 h.

Pharmaco Kinetics

- These agents ***require*** **loading doses** for ***quicker*** **antiplatelet effect.**
- ***Absorption*** of **Ticlopidine** ↓ **with food *but* not** with the **other agents.**
- ***Plasma protein binding***; ***extensively*** **bound** to plasma proteins.
- ***Metabolism***; by the cytochrome P450 (CYP) system.
  - **Clopidogrel** is a **prodrug** that ***requires activation*** via the cytochrome P450 enzyme isoform **CYP2C19**.
  - **Genetic polymorphism** of CYP 2C19 leads to a reduced clinical response in patients who are "poor metabolizers" of clopidogrel. Tests are currently available to identify poor metabolizers (In 2010, the FDA put a black box warning on Plavix® to make patients and healthcare providers aware that CYP2C19-poor metabolizers).
  - **Drugs that impair CYP2C19 function**, such as **Omeprazole**, should be ***used with caution*** pending clarification of the importance of CYP2C19 status (In 2009, the FDA issued a public-health warning about the possible interaction between clopidogrel and omeprazole).
  - ***Recent* meta-analysis study** (2015); In summary, suggest that the highly controversial interaction between PPIs (**Omeprazole**) and **Clopidogrel** observed in platelet aggregation studies has no clinical significance.
- ***Elimination***; Renal and fecal routes.

Therapeutic Uses

- **Clopidogrel** and **Prasugrel** *are approved for*;
  - **Non ST-elevation acute myocardial infarction**; **NSTEMI** (Unstable angina) & **ST-elevation myocardial infarction (STEMI)** ***including those*** **undergoing PCI**.
  - **Stroke** and **peripheral arterial disease**.
- **Ticlopidine** *is approved for*;
  - **Stroke *in patients with* transient ischemic attack** (**TIA**).
  - **Thrombotic stroke** and **coronary stent thrombosis**.
- **Ticagrelor** *is approved for*;
  - ***Prevention*** of **arterial thromboembolism *in patients with* unstable angina** & **acute MI *including those undergoing* PCI**.

Dose

- **Clopidogrel** ***loading dose***; 300-600 mg once, ***followed*** by of 75 mg daily.
- **Prasugrel**; ***loading dose*** 60 mg ***followed*** by 10 mg daily.
- **Ticlopidine**; ***loading dose*** 500 mg ***followed*** by 250 mg twice daily, for
- **Ticagrelor**; ***loading dose*** 180 mg ***followed*** by 90 mg twice daily.

- *Dual Antiplatelet Therapy* (*DAPT*);
  - ***Therapy with two antiplatelet agents***; **Thienopyridine agent** (e.g. clopidogrel) & **aspirin** to ***reduce*** the **risk of blood clots following coronary stent implantation**.
  - **Longer-term** dual antiplatelet therapy expectedly ***increased*** **bleeding**
  - **Severe and/or fatal bleeding** was ***uncommon***.
  - **DAPT dosing** strategies in acute coronary syndrome (ACS); see page no. 164.

Side Effects

- These agents ***can cause*** **prolonged bleeding** (no antidote).
- **Ticlopidine**;
  - **Nausea**, **dyspepsia**, and **diarrhea** in up to 20% of patients.
  - **Hemorrhage** in 5%.
  - **Leukopenia** in 1% (most seriously);
    - The leukopenia is detected by regular monitoring of the white blood cell count during the first 3 months of treatment.
  - **Thrombotic Thrombocytopenic Purpurea** (**TTP**);
    - Is a rare blood disorder characterized by clotting in small blood vessels of the body.
- **Clopidogrel**; has ***fewer adverse effects*** than **Ticlopidine**.
  - Neutropenia and TTP (very rare).
- ***N.B***; due to life-threatening hematologic adverse reactions, **Ticlopidine** is generally reserved for patients who are intolerant to other therapies.

FDA Warning

- **Prasugrel**; is ***contraindicated*** in ***patients with history of*** **transient ischemic attack (TIA)** ***or*** **stroke** ***because*** **of increased bleeding risk**.
- **Ticagrelor** and **Prasugrel** ***can cause serious*** and ***sometimes*** **fatal bleeding problems**.
- **Ticagrelor** ***diminished*** **effectiveness** ***with*** **concomitant use of aspirin doses above 100 mg**.

Glycoprotein IIb/IIIa Inhibitors

Abciximab (ReoPro®)	**Eptifibatide** (Integrilin®)	**Tirofiban** (Aggrastat®)

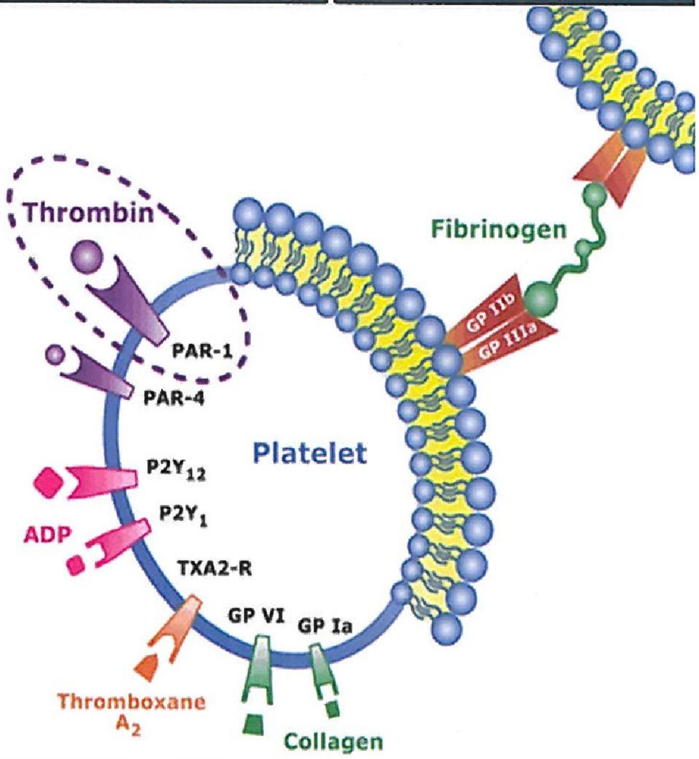
- Glycoprotein IIb/IIIa receptors on platelets bind to fibrinogen in the final common pathway of platelet aggregation.
- **Abciximab** [ab-SIKS-eh-mab] is a **chimeric monoclonal antibody**, ***inhibits*** the **GP IIb/IIIa receptor** ***and*** **von Willebrand factor**, it was the first agent approved in this class of drugs.
- **Eptifibatide** [ep-ti-FIB-ih-tide] is a **cyclic heptapeptide**, ***inhibits*** the **GP IIb/IIIa receptor**.
- **Tirofiban** [tye-roe-FYE-ban] is a **smaller molecule**, ***inhibits*** the **GP IIb/IIIa receptor**.
- All GP IIb/IIIa inhibitor agents should be used in combination with anticoagulant therapy and aspirin.
- *Uses*; These agents are **given IV**, ***along with*** **heparin** and **aspirin**, as an **adjunct to PCI** ***for the*** **prevention of cardiac ischemic complications**.
- *Dose*;
  - **Abciximab**; 0.25-mg/kg IV bolus, then 0.125 mcg/kg/min. (max 10 mcg/kg) for 12 hours.
  - **Eptifibatide**; 180-mcg/kg IV bolus × 2 (10 minutes apart); 2 mcg/kg/min. initiated after first bolus for 18–24 h. {maintenance dose in creatinine clearance < 50 ml/min. = 1 mcg/kg/min.}
  - **Tirofiban**; 25-mcg/kg IV bolus over 3 minutes, then 0.15 mcg/kg/minute for 18–24 hours.
- *Side effects*; The major side effects of these agents is **bleeding**, especially if used with anticoagulants.
- *N.B*; Oral formulations of IIb/IIIa antagonists are in various stages of development.

Protease-Activated Receptor-1 (PAR-1) Antagonists

Vorapaxar (Zontivity®)

Atopaxar

- **Vorapaxar** [vor-a-PAX-ar] is the ***first drug inhibit*** the **protease-activated receptor-1 (PAR-1)**, the primary receptor for thrombin.
- It is an ***antiplatelet agent***, designed to decrease the tendency of platelets aggregation.
- **Vorapaxar** approved by the FDA in 2014.
- ***Uses***; ***reduce*** **thrombotic cardiovascular events** ***in patients with a history of*** **MI** or ***with*** **peripheral arterial disease**.
- ***Dose***; **2.08 mg** orally ***once-daily***, ***should be*** **used with** daily **aspirin** ***and/or*** **clopidogrel** according to their indications or standard of care.
- ***Side effects***; ***increases*** the **risk of bleeding**, including life-threatening and fatal bleeding.
- **Atopaxar**; is the second PAR-1 antagonist, tended towards reducing major CV adverse events in acute coronary syndrome patients in a phase II trial.



Other Antiplatelet Drugs

Dipyridamole (Persantin®)

- **Dipyridamole** [dye-peer-ID-a-mole] is a **vasodilator** that also ***inhibits*** **platelet function** by ***inhibiting*** **adenosine uptake** and cGMP phosphodiesterase activity.
- ***Uses***; Dipyridamole by itself has ***little*** or ***no*** **beneficial effect**. ***Therefore***;
  - ***Used*** in **combination** ***primarily*** **with aspirin to prevent cerebrovascular ischemia** ⇨ **Aggrenox®** (aspirin/extended-release Dipyridamole capsules)
  - ***Used*** in **combination** ***with*** **warfarin** ***for*** **primary prophylaxis of thromboemboli** ***in patients with*** **prosthetic heart valves**.
- ***Side effects***; Headache and can lead to orthostatic hypotension (especially if administered IV).

Cilostazol (Pletal®)

- **Cilostazol** [sill-AH-sta-zole] is a ***newer*** **phosphodiesterase type III inhibitor** that ***promotes*** **vasodilation** (↑ cAMP) and ***inhibition*** of **platelet aggregation**.
- **Cilostazol** is ***extensively metabolized*** in the liver by the CYP3A4, 2C19 and 1A2 isoenzymes.
- ***Uses***; It is approved to ***reduce*** **the symptoms of intermittent claudication**.
  - **Intermittent Claudication**; is a symptom that describes muscle pain (ache, cramp, numbness or sense of fatigue), classically in the calf muscle, which occurs during exercise, such as walking, and is relieved by a short period of rest. It is classically associated with early-stage ***peripheral artery disease***, and can progress to critical limb ischemia unless treated or risk factors are modified.
- ***Side effects***; **Headache**, **GI side effects** (diarrhea, abnormal stools, dyspepsia, and abdominal pain) and **palpitation**.
- ***FDA warning***; **Cilostazol** is ***contraindicated*** in **patients with congestive heart failure**.
- ***Drug interactions***; **Itraconazole**, **Erythromycin**, **Ketoconazole**, **Diltiazem**, **Omeprazole** and **Grapefruit juice**.

- 2015: meta-analyses study. The results: long-term (12 months or longer) dual antiplatelet therapy with clopidogrel and aspirin do NOT appear to change the overall risk of death when compared to short-term (6 months or less) clopidogrel and aspirin or aspirin alone.

Antihemorrhagic Agents

Vitamin K (konakion®)

- **Vitamin K** is an essential factor to a hepatic gamma-glutamyl carboxylase that adds a carboxyl group to glutamic acid residues on factors II, VII, IX and X, as well as Protein S, Protein C and Protein Z.
- ***Two natural forms exist***: vitamins K_1 and K_2;
    - **Vitamin K_1** (**Phytonadione**) [fye toe na DYE own] is synthesized by plants and is found in highest amounts in green leafy vegetables.
    - **Vitamin K_2** (**Menaquinone**) is found in human tissues and is synthesized by intestinal bacteria.
- **Vitamins K_1** and **K_2** is a ***fat-soluble*** require bile salts for absorption from the intestinal tract.
- **Vitamin K_1** is ***available clinically*** in **oral** and **parenteral** ***forms***.
- ***Onset of effect*** is delayed for **6 hours** but the ***effect is complete*** by **24 hours**.
- ***Administration***; orally, SC, IM and IV.
- ***FDA warning***; IV administration of vitamin K_1 ***should be*** **very slowly**, not exceeding 1 mg/minute, **Severe hypersensitivity reactions**, including **anaphylactic reactions** and **deaths** have been reported following parenteral administration. The majority of these reported events occurred following IV administration, IV route should be restricted to those situations where another route is not feasible.
- ***Uses***; ***Treating*** **bleeding problems** caused by low vitamin K blood levels or decreased vitamin K activity, It may also be used to **treat or prevent certain bleeding problems in newborns**.
- ***Dosage Guidelines***;

Newborns prophylaxis	0.5 - 1 mg IM within 1 hour of birth
Newborns treatment	1 mg SC or IM
Usually adult dose	2.5 mg - 10 mg
Prothrombin deficiency due to warfarin	up to 25 mg
Prothrombin deficiency due to other causes	2.5 mg - 25 mg

Aminocaproic Acid (Amicar®) | Tranexamic Acid (Cyklokapron®)

- **Aminocaproic** [a-mee-noe-ka-PROE-ic] **acid** or **Tranexamic** [tran-ex-AM-ic] **acid** are ***antifibrinolytic drugs***.
- **Aminocaproic acid** (**EACA**) were first described in 1957 which, it is chemically ***similar*** to the **amino acid lysine**. **Tranexamic acid** is an ***analogue of*** **Aminocaproic acid** and has the ***same*** **properties** and **10 times** ***more potent*** than **Aminocaproic acid**.
- ***Mechanism***; ***Competitively inhibits*** **plasminogen activation**.
- ***Both agents*** are **synthetic, orally active** and **excreted in the urine**.
- ***Uses***;
    - **Adjunctive therapy in haemophilia** (is a group of hereditary genetic disorders that impair the body's ability to control blood clotting).
    - **Bleeding from fibrinolytic therapy**.
    - **Prophylaxis for re-bleeding from intracranial aneurysms.**
    - **Postsurgical GI bleeding, post-prostatectomy bleeding** and **bladder hemorrhage**.
    - **Tranexamic acid**; ***used as first-line*** **nonhormonal treatment of dysfunctional uterine bleeding (heavy menstrual bleeding or menorrhagia)**, ***dose***; 650 mg three times daily for five days during menses.
- ***Dose***;
    - **EACA**; ***For acute bleeding syndromes***; 5 g during the first hour of treatment, followed by a continuing rate 1 g per hour. This method of treatment would ordinarily be continued for about 8 hours or until the bleeding situation has been controlled.
    - **Tranexamic acid**; short-term use (2-8 days) ***in patients with haemophilia*** to reduce/prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction; **10 mg/kg IV 3 to 4 times daily**.
- ***Side effects***; Risk of intravascular thrombosis, hypotension, myopathy, abdominal discomfort, diarrhea, and nasal stuffiness.

Ethamsylate or Etamsylate (Dicynone®)

- **Ethamsylate** [Et-am-sill-ate] is a *synthetic* ***antihaemorrhagic and angioprotective drug*** acting on the ***first step*** of haemostasis (endothelium-platelet interaction).
- ***Mechanism***; by ***improving*** **platelet adhesiveness** and ***restoring*** **capillary resistance**, it is able to ***reduce*** **bleeding time** and **blood losses** (***no*** **vasoconstrictor action**).
- ***Pharmacokinetics***;
    - ***Absorption***; is slowly absorbed from the GIT. After oral administration ethamsylate maximum plasma level is reached after 4 hours.
    - ***Plasma half-life***; about 3-7 h.
    - ***Excretion***; excreted **unchanged in urine.**
    - Etamsylate ***crosses*** the **placental barrier** (pregnancy category C).
- *Uses*;
    - ***Prevention*** and ***treatment*** of **pre- or postsurgical capillary haemorrhages.**
    - ***Prophylaxis*** and ***control*** of **blood loss from small blood vessels.**
    - ***Control*** **heavy menstrual periods** or those who suffer from **excessive bleeding due to an intrauterine contraceptive device.**
- *Dose*;
    - ***Before surgery***; 500-1000 mg, ***followed*** by 500 mg every 4-6 hours.
    - ***Usual adult dose***; 500 mg 3-4 times daily.
    - ***Usual children dose***; 250 mg 3-4 times daily.
- *Side effects*; GIT disturbance, nausea, headache, skin rash.

Plasma Fractions

- ***Deficiencies*** in **plasma coagulation factors** can ***cause*** **bleeding.**
- Spontaneous bleeding occurs when factor activity is less than 5–10% of normal.
- **Factor VIII deficiency** (classic haemophilia or haemophilia A) and **factor IX deficiency** (Christmas disease or haemophilia B) account for most of the heritable coagulation defects.
- **Concentrated *plasma fractions* are available for the treatment of these deficiencies.**
- Administration of plasma-derived, heat- or detergent-treated factor concentrates and recombinant factor concentrates are the standard treatments for bleeding associated with haemophilia.

Dried Factor VIII Fraction (8Y®)

- It is a ***concentrate*** of **Factor VIII** and **von Willebrand Factor** (**VWF**) ***prepared from*** **blood plasma** from screened donors and then heat-treated.
- *Uses*; IV injection, to ***prevent & treat*** **bleeding in patients with haemophilia A** (an inherited shortage of Factor VIII in the blood) or von Willebrand disease (VWD).
- *Dose*; 10-50 IU/kg body weight, doses may be repeated at intervals of 8, 12 or 24 hours, as required.
- *Warning*; Because this product is made from human blood, it may carry a **risk of transmitting infectious agents** and may cause **hypersensitivity** or **allergic reactions.**

Factor IX Complex (BEBULIN®)

- BEBULIN® is a nano-filtered and vapour heated is a purified, sterile, freeze-dried concentrate of the **coagulation factor IX** (Christmas factor) as well as **Factor II** and **Factor X** and ***low amounts*** of **Factor VII**. In addition, the product contains ***small amounts*** of **heparin.**
- *Uses*; ***prevention*** and ***control*** of **bleeding episodes in adult patients with haemophilia B** (congenital Factor IX deficiency or Christmas disease).
- *Dose*; (IV only) ***Minor bleeding***; 25-35 IU/kg once. ***Moderate***; 50-65 IU/kg every 24 hours twice or until adequate wound healing. ***Major***; 75-90 IU/kg every 24 hours 3-4 times or until adequate wound healing.
- *Warning*; **Hypersensitivity** or **allergic reactions** ***may occurs.***

Anti-Inhibitor Coagulant Complex Heat Treated (Autoplex®)

- Autoplex® is a sterile product prepared from pooled human plasma.
- The product is standardized by its ***ability*** to **correct the clotting time** of **Factor VIII deficient plasma** or Factor VIII deficient plasma which contains ***inhibitors*** to **Factor VIII.**
- *Uses*; **This product is to be used only in patients with inhibitors to Factor VIII *who are bleeding or are to undergo surgery.***

- ***Dose***; (IV only) 25-100 Hyland Factor VIII Correctional Units/kg of body weight, depending upon the severity of hemorrhage. If no hemostatic improvement is observed approximately 6 hours following the initial administration, the dosage should be repeated.
- ***Warning***; Because this product is made from human blood, it may carry a risk of transmitting infectious agents and may cause **hypersensitivity** or **allergic reactions**.

Anti-Inhibitor Coagulant Complex (FEIBA-$^{NF®}$)

- **FEIBA** (**F**actor **E**ight **I**nhibitor **B**ypass **A**ctivity); is a nano-filtered and vapour heated, is a freeze-dried sterile human plasma fraction with **Factor VIII inhibitor bypassing activity**.
- It contains Factors II, IX, and X, mainly non-activated and Factor VII mainly in the activated form. The product contains Factor VIII inhibitor bypassing activity and Prothrombin Complex Factors.
- ***Uses***; *Control* of **spontaneous bleeding episodes** ***or to cover*** **surgical interventions** in **haemophilia A and haemophilia B patients with inhibitors**.
- ***Dose***; (IV infusion) 50-100 Units of FEIBA^{NF}/kg/day is recommended.
- ***Warning***; **Hypersensitivity** or **allergic reactions** or **thromboembolic event** or **risk of transmitting infectious agents**.

Recombinant Human Coagulation Factor VIIa (rFVIIa) (NovoSeven®)

- NovoSeven® is structurally similar to human plasma-derived Factor VIIa.
- ***Uses***; ***Control*** **bleeding episodes** and to ***prevent*** **excessive bleeding during surgery** in people who have;
    - **Inhibitors to clotting factors VIII** or **IX**.
    - **Congenital FVII deficiency**.
    - **Glanzmann's Thrombasthenia** (is an abnormality of the platelets, in which the platelets contain defective or low levels of glycoprotein IIb/IIIa) which cannot be treated effectively with platelet transfusions.
- ***Dose***; 35-120 micrograms/kg (usually 90 micrograms/kg) given every two hours by bolus infusion until hemostasis is achieved, or until the treatment has been judged to be inadequate.
- ***Warning***; **thromboembolic event** ***may occurs***.

Cryoprecipitate (CRYO)

- The ***main constituents*** of **Cryoprecipitate** are **Factors VIII** and **XIII**, **von Willebrand Factor** and **Fibrinogen**.
- ***Uses***; **Haemophilia**, **von Willebrand disease** and **hypofibrinogenaemia** (low fibrinogen levels).
- ***Dose***; 1 U/5kg patient weight repeat if needed.
- ***Warning***; **Hypersensitivity** or **allergic reactions** or **risk of transmitting infectious agents**.

Other Agents

Aprotinin (Trasylol®)

- **Aprotinin** [a-proe-TYE-nin] ***also known as*** **bovine pancreatic trypsin inhibitor (BPTI)** ***or*** **serine protease inhibitor (serpin)**.
- ***Act by inhibits*** **several serine proteases**, specifically **trypsin**, **chymotrypsin**, **plasmin** and **kallikrein**; ***leads to*** ⇨ **inhibition of fibrinolysis**.
- ***Used*** to **reduce bleeding during complex surgery** (e.g. **cardiopulmonary bypass**).
- ***Warning***; Aprotinin may cause severe and sometimes ***fatal allergic reactions*** (**anaphylaxis**).

Octreotide (Sandostatin®)

- **Octreotide** [ok-TREE-oh-tide] is **Somatostatin** (growth hormone-inhibiting hormone) **analogue**.
- **Octreotide** is often given as an infusion for management of **acute haemorrhage from esophageal varices** in **liver cirrhosis**.
- Details see pages no. 882.

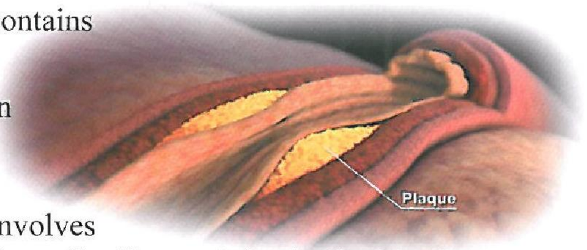
Desmopressin (Minirin®) | Terlipressin (Teripress®)

- They are a synthetic replacement for vasopressin, (Details; see page no. 894)
- **Desmopressin** ***increases*** the **factor VIII activity** of patients with ***mild*** **haemophilia** A or **von Willebrand disease** ***in*** preparation for ***minor*** **surgery** such as **tooth extraction**.
- **Terlipressin**; ***used in*** **acute haemorrhage from esophageal varices** in **liver cirrhosis**.

Hyperlipidemia

➢ Overview:-

- **Plasma lipids** are transported in complexes *called* **lipoproteins**.
- **Lipoprotein**; is a biochemical assembly that contains *both* **proteins** and **lipids**.
- **Metabolic disorders** that involve elevations in any lipoprotein species are termed **hyperlipoproteinemias** or **hyperlipidemias**.

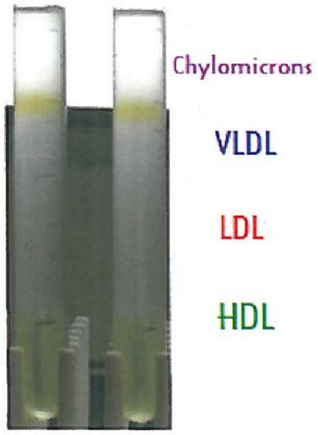


- **Hyperlipidemia** or **Hyperlipoproteinemia**; involves ***abnormally* elevated levels** of ***any* or *all* lipids *and/or* lipoproteins in the blood**.
- The two major clinical syndrome of hyperlipidemias are **acute pancreatitis** and **atherosclerosis**.
- **Atherosclerosis** is ***correlated*** with **elevated** levels of low-density lipoprotein cholesterol (**LDL-C**; bad cholesterol) and **triglycerides** and low levels of high-density lipoprotein cholesterol (**HDL-C**; good cholesterol).
- ***During fasting*** (12-hour fast; no food or drink, except water), **total plasma lipids concentration *range from* 360-820 mg/dl**. ***They includes***:

Lipid	Adult Desirable Value
Total Cholesterol	Less than 200 mg/dl
Triacylglycerol; TAG (*or* Triglycerides; TGs)	Less than 150 mg/dl
Phospholipids (PPL)	125-275 mg/dL
Free Fatty Acids (FFA)	8-25 mg/dl

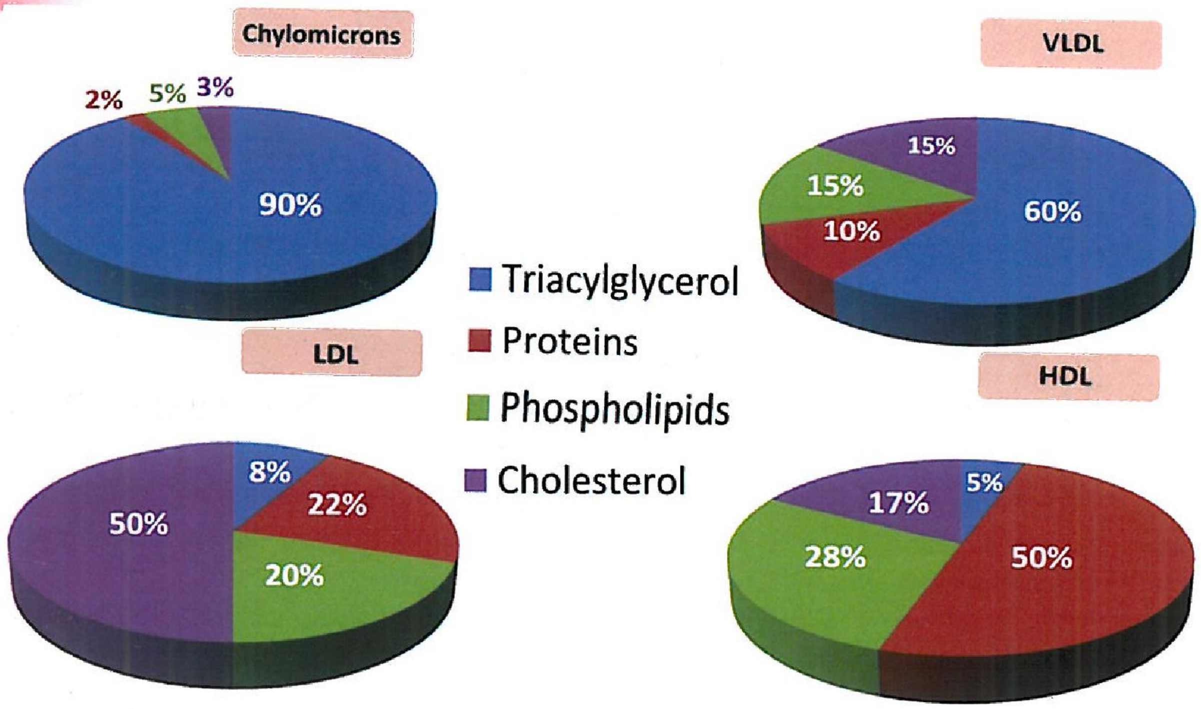
➢ Plasma Lipids:-

- **Lipids** *alone* are water insoluble. Thus, they *cannot* be transported in plasma.
- **Lipids** are ***conjugated*** to **proteins** to ***form*** **lipoproteins**, which are water soluble and ***can*** be transported in plasma.
- These proteins are ***synthesized by*** the **liver** and ***called*** **Apo-lipoproteins** (Apo-proteins), they are **six classes** of apolipoproteins and **several sub-classes**;
  - **A** (apo A-I, apo A-II, apo A-IV, and apo A-V).
  - **B** (**apo B-$_{48}$** and **apo B-$_{100}$**).
  - **C** (apo C-I, apo C-II, apo C-III, and apo C-IV).
  - **D, E** and **H**.
- **Separation of Plasma Lipoproteins;**
  - ***By* ultracentrifugation method**;
    - *Separation according to density*:
      - **1: Chylomicrons** (*largest*).
      - **2: Very Low Density Lipoproteins; VLDL.**
      - **3: Low Density Lipoproteins; LDL.**
      - **4: High Density Lipoproteins; HDL** (*Smallest*).
  - *Separation may occur by* **electrophoresis method**.

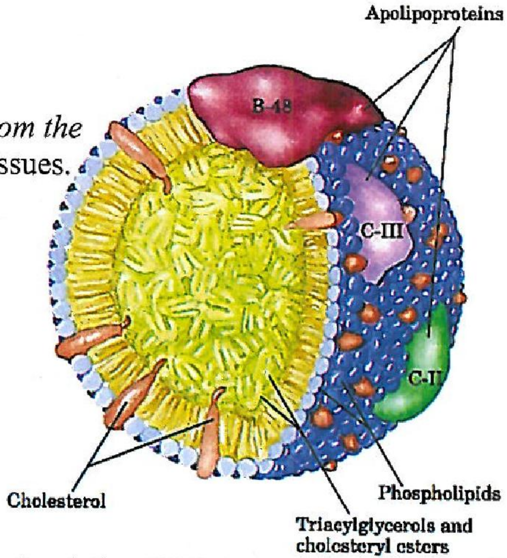


Ultracentrifugation

Plasma Lipoprotein	Source	Main lipid	Apo-lipoproteins	
Chylomicrons	Intestine	Triacylglycerol (TAG)	2%	A, B-$_{48}$, C & E
VLDL	Liver	Triacylglycerol (TAG)	10%	B-$_{100}$, C & E
LDL	Blood from VLDL	Cholesterol and phospholipids	22%	B-$_{100}$
HDL	Liver		50%	A, C, D & E
FFA-Albumin	Adipose tissue	FFA	99%	Albumin

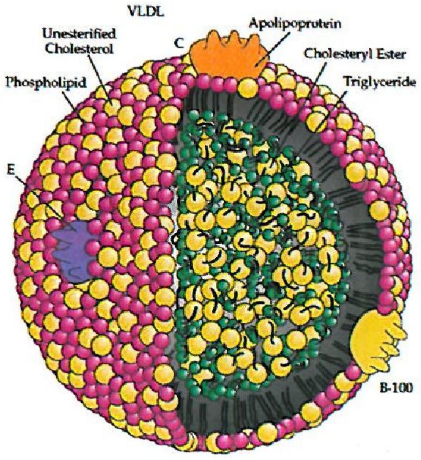


➢ Chylomicrons:-


Apolipoproteins
B-48
C-III
C-II
Cholesterol
Phospholipids
Triacylglycerols and cholesteryl esters

- **Site of synthesis**; Intestinal mucosa.
- **Functions**; Chylomicrons transport dietary lipids *from the* intestine to the blood to the peripheral tissues.
- **Structure**;
  - **Lipids**;
    - Triglycerides (~ 90%).
    - Phospholipids (~ 5%).
    - Cholesterol (~ 3%).
  - **Proteins** (~ 2%); Apo A, B-$_{48}$, E & C.
- **Metabolism**;
  - The particles released by intestinal mucosal cells are called **nascent chylomicrons** and contains apolipoprotein B-$_{48}$.
  - When it reaches the plasma, it *receives* from circulating HDL two apolipoproteins E and C and converted into **mature chylomicrons**.
  - The **triacylglycerol** component of chylomicrons well be ***hydrolyzed into*** **glycerol** and **fatty acids**. This reaction is catalyzed by ***lipoprotein lipase*** **(LPL*)*** ***enzyme*** which is *activated by* **apo C-II**.
  - After hydrolysis of TG, the chylomicrons particles begin to ***shrink***. In addition, the Apo C-II ***returns to*** HDL.
  - The remaining particles are called **chylomicron remnants**.

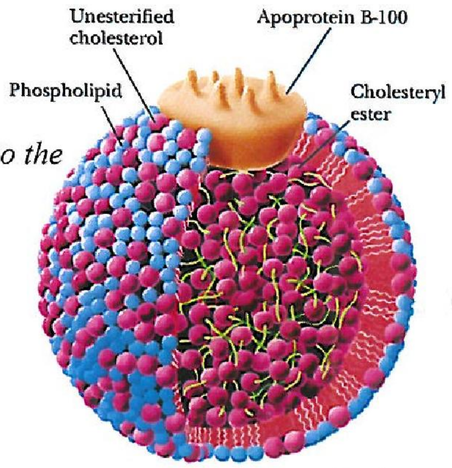
➢ Very Low Density Lipoproteins (VLDL):-


VLDL
Unesterified Cholesterol
C
Apolipoprotein
Cholesteryl Ester
Phospholipid
Triglyceride
E
B-100

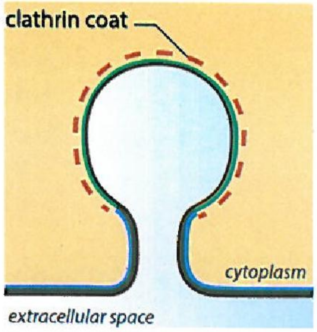
- **Site of synthesis**; Liver.
- **Functions**; VLDL carries lipids *from* liver *to the* blood *to the* peripheral tissues.
- **Structure**;
  - **Lipids**;
    - Triacylglycerol (~ 60%).
    - Cholesterol (~ 15%).
    - Phospholipids (~ 15%).
  - **Proteins** (~ 10%); Apo B-$_{100}$, Apo E and Apo C.

- **Metabolism**;
  - The particles *released from* the **liver** are called **nascent VLDL** and *contain* **apo B_{100}.**
  - When it reaches the plasma, it *receives* from circulation HDL two apolipoproteins E and C and converted to **mature VLDL**.
  - The triacylglycerol (TG) component of VLDL well be ***hydrolyzed into* glycerol** and **fatty acids**. This reaction is catalyzed by ***lipoprotein lipase (*LPL*) enzyme***⇨ which is *activated by* apo C-II.
  - After hydrolysis of TG, the particles begin to ***shrink***. The remaining particles are called **intermediate density lipoproteins (IDL)**.
  - **IDL** is converted into **LDL** by transferring phospholipids, apo CII and apo E to HDL.
  - LDL are removed from circulation by tissues as muscle (*see LDL metabolism*).
  - **VLDL** particles also *transfer* phospholipids (PPLs) and triacylglycerol (TG) to HDL, *at the same time* **HDL** *transfer* cholesterol esters (CE) to **VLDL**. These reactions are catalyzed by ***Cholesterol ester transfer protein***.

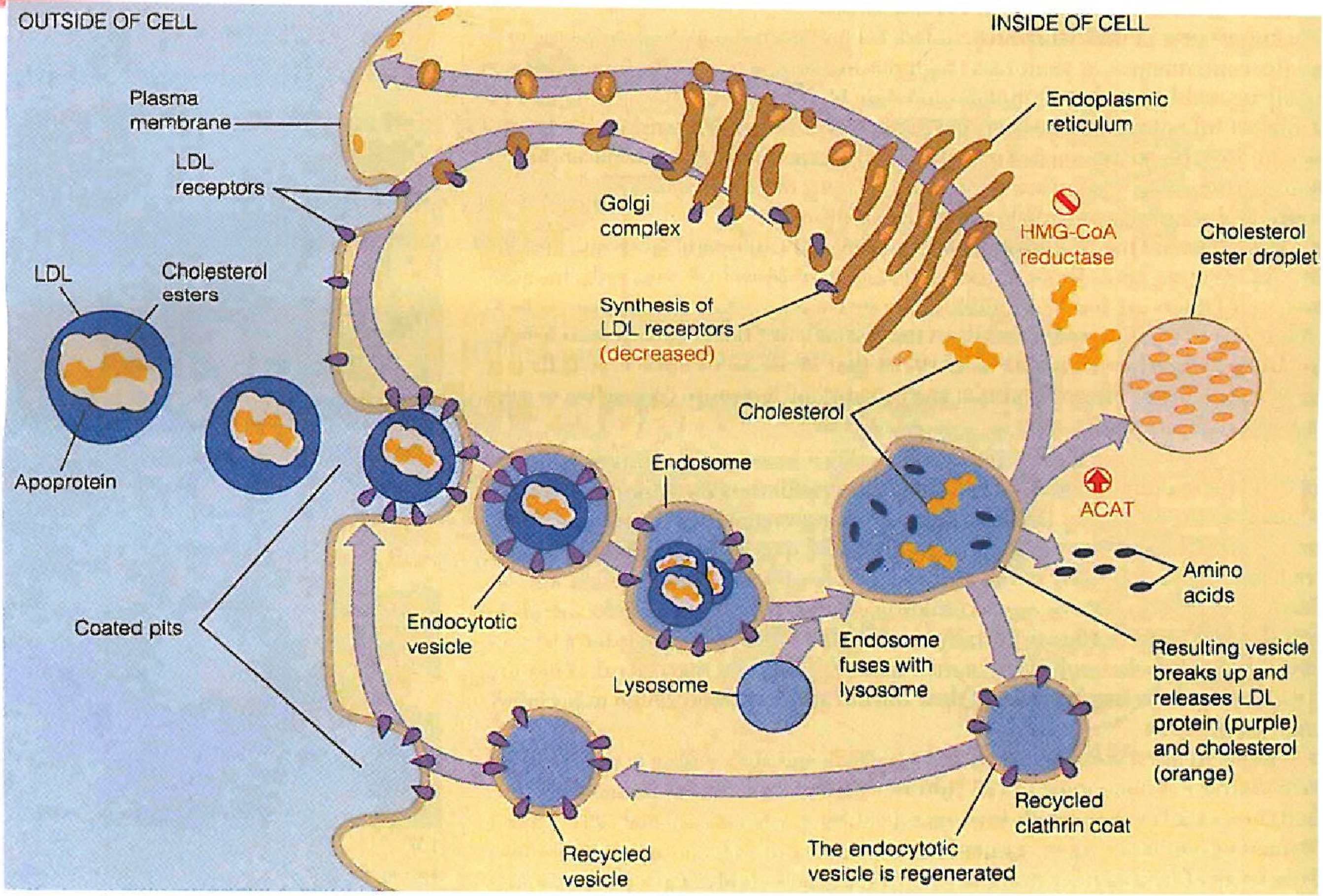
➢ Low Density Lipoproteins (LDL):-



- **Site of synthesis**; Circulation (*from* VLDL).
- **Function;*** *Transfer of* cholesterol *from the* liver *to the* peripheral tissues.
- **Structure;***
  - **Lipids**;
    - Cholesterol (~ 50%).
    - Phospholipids (~ 20%).
    - Triglycerides (~ 8%).
  - **Proteins** (~ 22%); Apo B-$_{100}$.
- **Metabolism**;
  - The **LDL receptors** on the cell membrane are negatively charged glycoprotein molecules, made by the DNA of the cell. They are grouped in pits in cell membranes. The intracellular site of pits coated with a protein called **Clathrin**.



  - After binding with receptors, the LDL are internalized as intact particles by **endocytosis**.
  - The vesicle containing the LDL rapidly lose its clathrin coat and fuses with other similar vesicles, forming large vesicle called **endosomes** (*See photo; next page*).
  - The pH of the contents of endosomes falls, allowing separation of the LDL from its receptors, then migrate to one side of the endosomes while LDL stays free within the lumen of the vesicle.
  - The receptor can be returned to the cell membrane. The lipoprotein remnants are hydrolyzed by **lysosomal enzyme** releasing cholesterol, amino acids, phospholipids and fatty acids.
  - ***If cell contains oversupply of cholesterol***;
    - ***Inhibits* HMG-CoA** (3-hydroxy-3-methylglutaryl-coenzyme A) **reductase** enzyme activity ***so*** that **cholesterol synthesis** well be ***decreased***.
    - ***Stimulate*** a liver enzyme called **Acyl CoA cholesterol acyl transferase** (**ACAT**). ACAT transfer a fatty acid from fatty acyl CoA to cholesterol to form cholesteryl ester that can be stored inside the cell.
    - ***Inhibit*** the **synthesis of new LDL receptor**, so that further entry of LDL cholesterol into the cell is ***limited***.

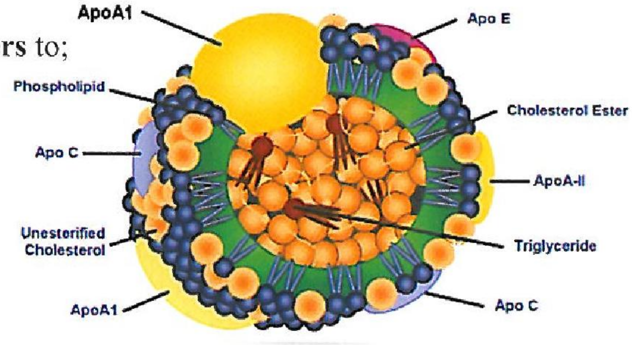

OUTSIDE OF CELL
INSIDE OF CELL
Plasma membrane
LDL receptors
LDL
Cholesterol esters
Apoprotein
Coated pits
Golgi complex
Endoplasmic reticulum
HMG-CoA reductase
Cholesterol ester droplet
Synthesis of LDL receptors (decreased)
Cholesterol
Endosome
ACAT
Amino acids
Endocytotic vesicle
Lysosome
Endosome fuses with lysosome
Resulting vesicle breaks up and releases LDL protein (purple) and cholesterol (orange)
Recycled clathrin coat
The endocytotic vesicle is regenerated
Recycled vesicle

➢ High Density Lipoproteins (HDL):-

- **Site of synthesis**; Liver.
- **Function**;*
  1: ***Remove*** **free** (unesterified) **cholesterol** from extra hepatic tissues and esterifying it, using a plasma enzyme called **Lecithin Cholesterol Acyl Transferase (LCAT)** [The apo A-I of HDL activates LCAT].

  2: Act as ***reservoir*** of **apo C-II** that is *transferred to* **chylomicrons** and **VLDL** to *activate* **lipoprotein lipase (LPL) enzyme.**

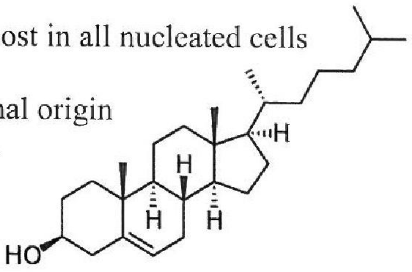
  3: HDL particles ***carry*** **cholesterol esters** to;
    - **VLDL** and **LDL**
    - **Liver** (HDL is hydrolyzed and cholesterol released).


ApoA1
Apo E
Phospholipid
Cholesterol Ester
Apo C
ApoA-II
Unesterified Cholesterol
Triglyceride
ApoA1
Apo C

- **Structure**;*
  - **Lipids**;
    - Phospholipids (~ 28%).
    - Cholesterol (~ 17%).
    - Triglycerides (~ 5%).
  - **Proteins** (~ 50%); Apo A, C and E.
- **Metabolism**;
  - A newly secreted HDL are *disc shaped* particles containing mainly unesterified cholesterol and phospholipids.
  - Once the free cholesterol is taken up, it's immediately esterified by **LCAT**. The resulting cholesterol ester is very hydrophobic, so it remains in HDL and cannot be transferred to peripheral tissues.
  - The liver takes up HDL particles, where the cholesteryl esters are hydrolyzed.
  - ***The released cholesterol my undergo***;
    - Binding with apo-proteins to form lipoproteins.
    - Converting to bile acids.
    - Secreted into the bile to be removed from the body.

➢ Cholesterol:-

- **Name**;
  - It is an **animal sterol**, from the Greek ***chole-*** (**bile**) and ***stereos*** (**solid**) followed by the chemical suffix ***-ol*** for an **alcohol**.
- **Source**;
  - **Endogenous**; Cholesterol is formed in the body almost in all nucleated cells from Acetyl-CoA.
  - **Exogenous**; Cholesterol occurs only in food of animal origin such as egg yolk, meat, liver and brain.

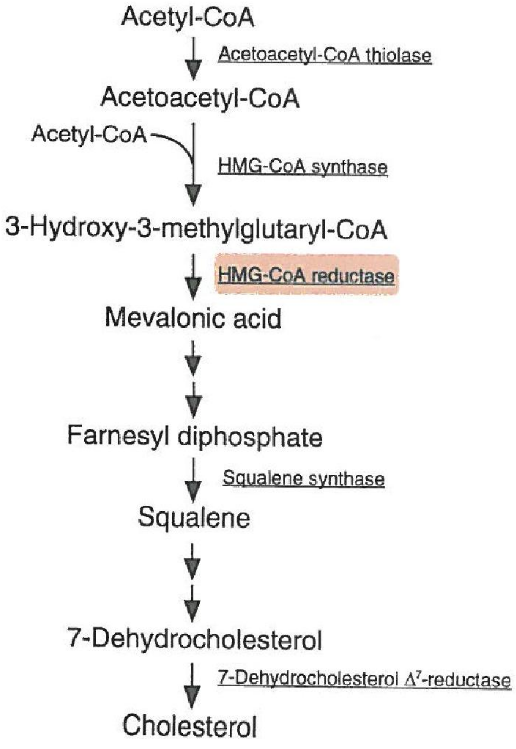


- **Diet**;
  - **Healthy diet**; no more than 300 mg of cholesterol a day.
  - A typical **egg contains** ~ 200 mg of cholesterol.
  - Eggs are high in cholesterol, ***but*** the effect of egg consumption on blood cholesterol is minimal when compared with the effect of trans-fats and saturated fats.
  - In a review of ***studies*** in which volunteers were fed eggs, researchers found that lowering the amount of dietary cholesterol by 100 mg a day resulted in only a 1% reduction in blood cholesterol levels.
  - ***Studies*** suggest that only about 30% of people are particularly susceptible to the effects of dietary cholesterol on blood cholesterol levels.

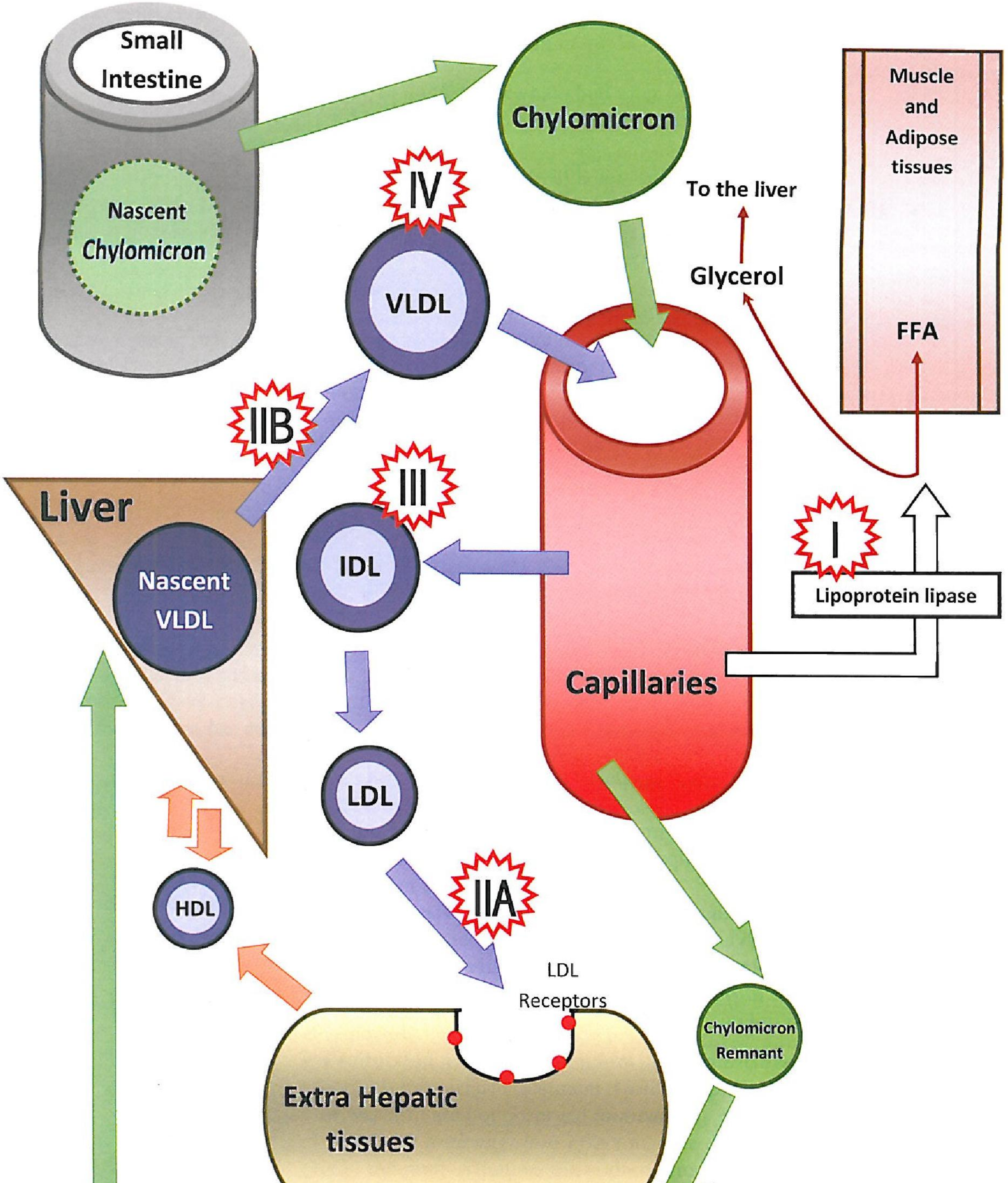
Cholesterol Trick

  - ***Previously***, the Dietary Guidelines for Americans recommended that cholesterol intake be limited to no more than 300 mg/day. The **2015 Dietary Guidelines Advisory Committee** (**DGAC**) will not bring forward this recommendation ***because*** available evidence shows no appreciable relationship between consumption of dietary cholesterol and serum cholesterol. The committee found strong evidence that replacing saturated fat with unsaturated fat would lower LDL cholesterol levels, and that low-fat diets which replace saturated fat with carbohydrates would lower LDL and HDL cholesterol levels. Trans-fats have been shown to reduce levels of HDL while increasing levels of LDL.
- **Function**;
  - **Hormone production**; Cholesterol plays a part in producing hormones such as **estrogen**, **testosterone**, **progesterone**, **aldosterone** and **cortisone**.
  - **Vitamin D production**; Vitamin D is produced when the sun's UV rays reach the human skin surface.
  - **Bile production**; Cholesterol produces bile acids which aid in digestion and vitamin absorption (fat-soluble vitamins, A, D, E, and K).
  - **Cell membrane support**; Cholesterol plays a very important part in both the creation and maintenance of human cell membrane.
- **Biosynthesis**;
  - **Location**; Cytosol (liver is the major site).
  - **HMG-CoA** (3-hydroxy-3-methylglutaryl-coenzyme A) **reductase enzyme** is the ***key enzyme*** for **cholesterol synthesis**.
  - ***Regulation of cholesterol synthesis***;

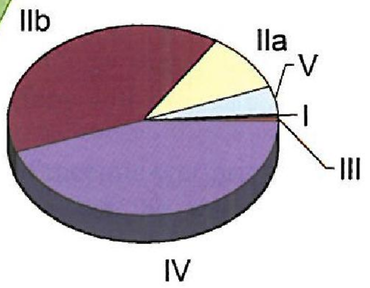
1) **Feedback inhibition**; Cholesterol act as feedback inhibitor of HMG-CoA reductase enzyme, i.e. decrease more cholesterol synthesis.
2) **Feedback regulation**; Cholesterol inhibits HMG-CoA reductase gene, this decrease transcription and synthesis of HMG Co-A reductase.
3) **Glucagon *inhibits*** HMG CoA reductase, while **insulin *stimulate*** HMG CoA reductase.
4) **Drugs**; e.g. **Statins** inhibit HMG CoA reductase.



➢ Metabolism of Plasma Lipoproteins and Related Genetic Diseases:-


Small Intestine
Nascent Chylomicron
Chylomicron
Muscle and Adipose tissues
To the liver
Glycerol
FFA
IV
VLDL
IIB
Liver
Nascent VLDL
III
IDL
I
Lipoprotein lipase
Capillaries
LDL
IIA
HDL
LDL Receptors
Chylomicron Remnant
Extra Hepatic tissues
By: Dhshan

- Type I [Familial Hyperchylomicronemia].
- Type IIA [Familial Hypercholesterolemia].
- Type IIB [Familial Combined (Mixed) Hyperlipidemia].
- Type III [Familial Dysbetalipoproteinemia].
- Type IV [Familial Hypertriglyceridemia].
- Type V [Familial Mixed Hypertriglyceridemia].



Relative prevalence of familial hyperlipidemias

➢ Hyperlipidemia Classification:-

A) **Familial** (*or* **Primary**) **Hyperlipidemias** (*according to the Fredrickson classification*);

Type I [Familial Hyperchylomicronemia]

- Massive fasting hyperchylomicronemia, even following normal dietary fat intake, resulting in greatly elevated serum TG levels.
- Deficiency of lipoprotein lipase or deficiency of normal apolipoprotein CII (rare).
- Type I is not associated with an increase in coronary heart disease.
- Treatment: Low-fat diet. No drug therapy is effective for Type I hyperlipidemia.
- Prevalence; 1 in 1,000,000.

↑ Chylomicron

Type IIA [Familial Hypercholesterolemia]

- Elevated LDL with normal VLDL levels due to a block in LDL degradation. This results in increased serum cholesterol but normal TG levels.
- Caused by defects in synthesis or processing of LDL receptors.
- Coronary heart diseases are greatly accelerated.
- Treatment: Diet. Drug therapy: Cholestyramine and niacin or statin.
- Prevalence; 1 in 500.

↑ LDL

Type IIB [Familial Combined (Mixed) Hyperlipidemia]

- Similar to type IIA but VLDL is also increased, resulting in elevated serum TG as well as cholesterol levels.
- Caused by overproduction of VLDL by the liver.
- Treatment: Diet. Drug therapy: Cholestyramine and niacin or statin.
- Prevalence; 1 in 100.

↑ VLDL and LDL

Type III [Familial Dysbetalipoproteinemia]

- Serum concentration of IDL are increased resulting in increased TG and cholesterol levels.
- Caused by overproduction or underutilization of IDL (mutant APO E).
- Xanthomas (*see symptoms*) and ↑ vascular diseases in patient with middle age.
- Treatment: Diet. Drug therapy includes niacin and fenofibrate or statin.
- Prevalence; 1 in 10,000.

↑ IDL

Type IV [Familial Hypertriglyceridemia]

- Increase VLDL while LDL is normal or decrease resulting in normal to elevated cholesterol and greatly ↑ TG.
- Caused by overproduction and/or decreased removal of VLDL and TG in serum.
- Patients with this disorder are frequently obese, diabetic and hyperuricemia.
- Treatment: Diet. If necessary, drug therapy includes niacin and/or fenofibrate.
- Prevalence; 1 in 100.

↑ VLDL

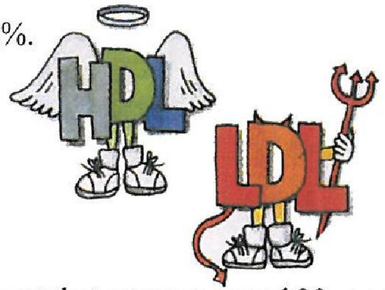
Type V [Familial Mixed Hypertriglyceridemia]

- Serum VLDL and Chylomicron are elevated, LDL is normal or decreased resulting in elevated cholesterol and greatly elevated TG levels.
- Caused by over production and ↓ clearance of VLDL and chylomicron in serum (usually it is genetic defect).
- Occur mainly in adults who are obese and/or diabetic.
- Treatment: Diet. If necessary, drug therapy; niacin, and/or fenofibrate or statin.
- Prevalence; 1 in 200.

↑ Chylomicron
VLDL

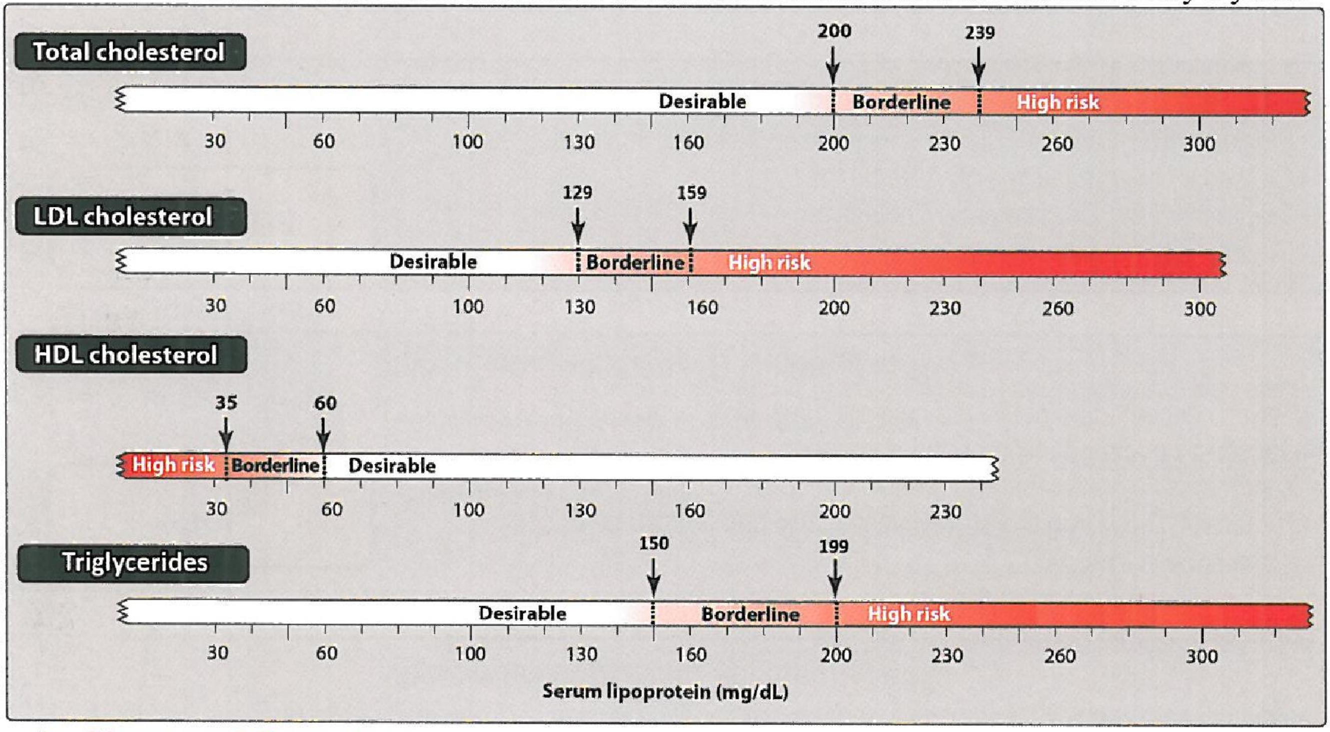
B) Acquired (*or* Secondary) Hyperlipidemias;

- They may result in ***increased* risk** of premature **atherosclerotic cardiovascular disease (ASCVD)** or when associated with ***marked* hypertriglyceridemia** may ***lead to* pancreatitis** and other complications.
- *Causes*;
  - ***The most common causes***;
    - Diabetes mellitus.
    - Use of drugs *such as* diuretics, β-blockers and estrogens.
  - ***Dietary causes include***;
    - Fat intake per total calories greater than 40%.
    - Saturated fat intake per total calories greater than 10%.
    - Excessive alcohol intake.
  - ***Other conditions include***;
    - Hypothyroidism.
    - Renal failure.
    - Nephrotic syndrome.



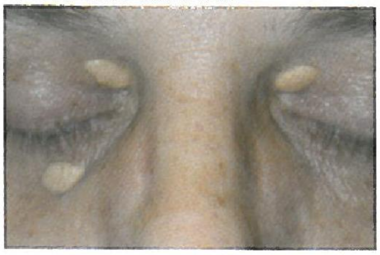
➢ Plasma Cholesterol Levels:-

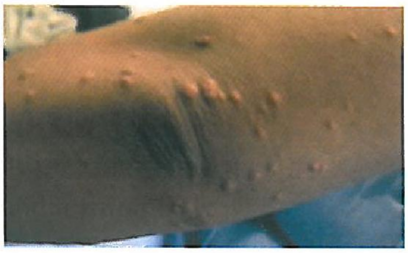
- The National Cholesterol Education Program guidelines suggest that everyone aged 20 years and older should have their blood cholesterol level measured at least once every 5 years.

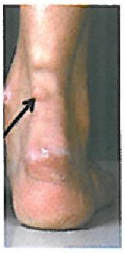


➢ Signs and Symptoms:-

- **High cholesterol levels *normally* do not cause any symptoms (asymptomatic).**
- ***Some types*** of hypercholesterolemia lead to specific physical findings. More common in **familial hypercholesterolemia** may be associated with;
  - **Xanthelasma Palpebrarum** [ZAN-theh-LAZ-mah]; Yellowish patches around eyelids.
  - **Arcus senilis**; white or gray discoloration of the peripheral cornea.
  - **Xanthomata**; deposition of yellowish cholesterol-rich material in the tendons, palms, knees and elbows.







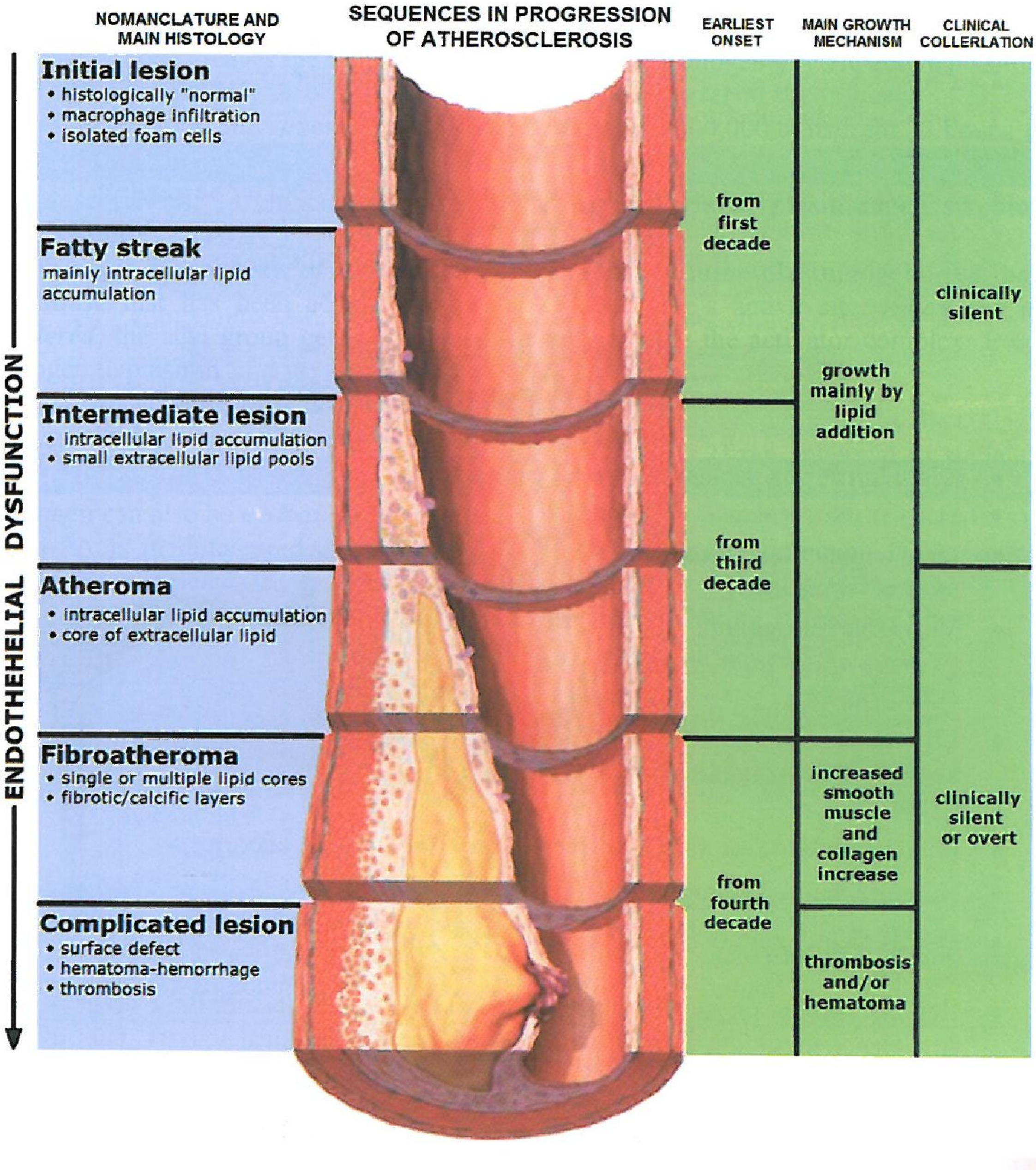
Atherosclerosis

➢ Background:-

- The word **atherosclerosis** is of Greek origin means, focal accumulation of lipid (i.e., **athere** [gruel]) and thickening of arterial intima (i.e., **sclerosis** [hardening]) *also known as*; **atherosclerotic cardiovascular disease** (**ASCVD**) or **hardening of the arteries**.
- *Definition*; is a condition in which **plaque *builds-up* inside the arteries**.
- *Characterise*;
  - **Endothelial dysfunction.**
  - **Vascular inflammation.**
  - **Lipid build-up**, *includes*; cholesterol, fatty substances, cellular waste, Ca^{2+} and fibrin.
- It is the ***main cause*** of **coronary artery disease** (**CAD**), in which atherosclerotic changes are present within the walls of the coronary arteries.
- ***Approximately*** 14 million Americans have CAD. Each year; 1.5 million individuals develop acute myocardial infarction, a third of whom die.

➢ Pathophysiology:-

- The build-up of an **atheromatous plaque** is a ***slow process***, developed over a period of **several years**, usually10-15 years for full development.
- *Simple Pathophysiology Process*;


NOMANCLATURE AND MAIN HISTOLOGY
SEQUENCES IN PROGRESSION OF ATHEROSCLEROSIS
EARLIEST ONSET
MAIN GROWTH MECHANISM
CLINICAL COLLERLATION
ENDOTHEHELIAL DYSFUNCTION
Initial lesion
• histologically "normal"
• macrophage infiltration
• isolated foam cells
Fatty streak
mainly intracellular lipid accumulation
Intermediate lesion
• intracellular lipid accumulation
• small extracellular lipid pools
Atheroma
• intracellular lipid accumulation
• core of extracellular lipid
Fibroatheroma
• single or multiple lipid cores
• fibrotic/calcific layers
Complicated lesion
• surface defect
• hematoma-hemorrhage
• thrombosis
from first decade
from third decade
from fourth decade
growth mainly by lipid addition
increased smooth muscle and collagen increase
thrombosis and/or hematoma
clinically silent
clinically silent or overt

1) ***Adherence*** of **monocytes** (a type of white blood cell) to the endothelium then migration to the sub-endothelial space and further activation into **monocyte-derived macrophages**.
2) **LDL** particles in blood plasma invade the endothelium and become ***oxidized***.

- ***N.B***; A complex set of biochemical reactions regulates the oxidation of LDL, involving enzymes and free radicals in the endothelium ⇨ damage to the endothelium ⇨ inflammatory response.

3) **Macrophages *ingest* oxidized LDL** slowly turning into large "**foam cells**".
4) **Foam cells** eventually ***die*** and further propagate the **inflammatory process**.
5) Formation of a **fibrous capsule** covering the fatty streak. Intact endothelium could prevent the proliferation by releasing nitric oxide.
6) In time, as cells die, this leads to **extracellular Ca^{2+}** deposits between the muscular wall and outer portion of the atheromatous plaques.

- ***N.B***; Platelet-derived growth factor, insulin-like growth factor, transforming growth factors alpha and beta, thrombin and angiotensin II are potent mitogens.

7) Although the disease process tends to be slowly progressive over decades, it usually remains asymptomatic until an **atheroma ulcerates**, which leads to immediate **blood clotting** at the site of atheroma ulcer. This triggers a cascade of events that leads to clot enlargement, which may quickly obstruct the flow of blood.

➢ Symptoms:-

- Atherosclerosis is **asymptomatic** for decades ***because*** the arteries enlarge at all plaque locations, there is no effect on blood flow.
- **Signs and symptoms *only occur* after severe narrowing** or **closure blood flow** (clot).
- **Complete** coronary artery **blockage *leads to* ischemia** of the myocardial muscle lead to **myocardial infarction**.

➢ Diagnosis:-

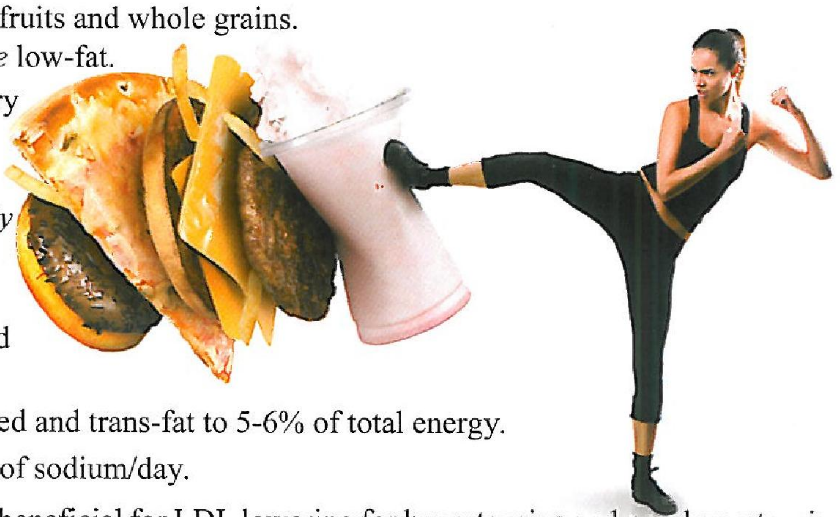
- ***Laboratory tests***: Lipid profile, thyroid function, CBC and blood glucose.
- ***Imaging studies***: Echocardiography, nuclear imaging, computed tomography, magnetic resonance imaging (MRI), coronary angiography and ultrasonography.

➢ Management:-

Lifestyle Modification

- ***Dietary recommendations to lower LDL includes***;

  - Diet high in vegetables, fruits and whole grains.
  - Dairy products *should be* low-fat.
  - Fish, legumes and poultry (*sources of protein*).
  - Vegetable oils and nuts (*sources of essential fatty acids; EFAs*).
  - Limitation of sugar sweetened beverages and red meats.
  - Reduce intake of saturated and trans-fat to 5-6% of total energy.
  - No more than 2,400 mg of sodium/day.
  - DASH dietary pattern is beneficial for LDL lowering for hypertensive and non-hypertensive.



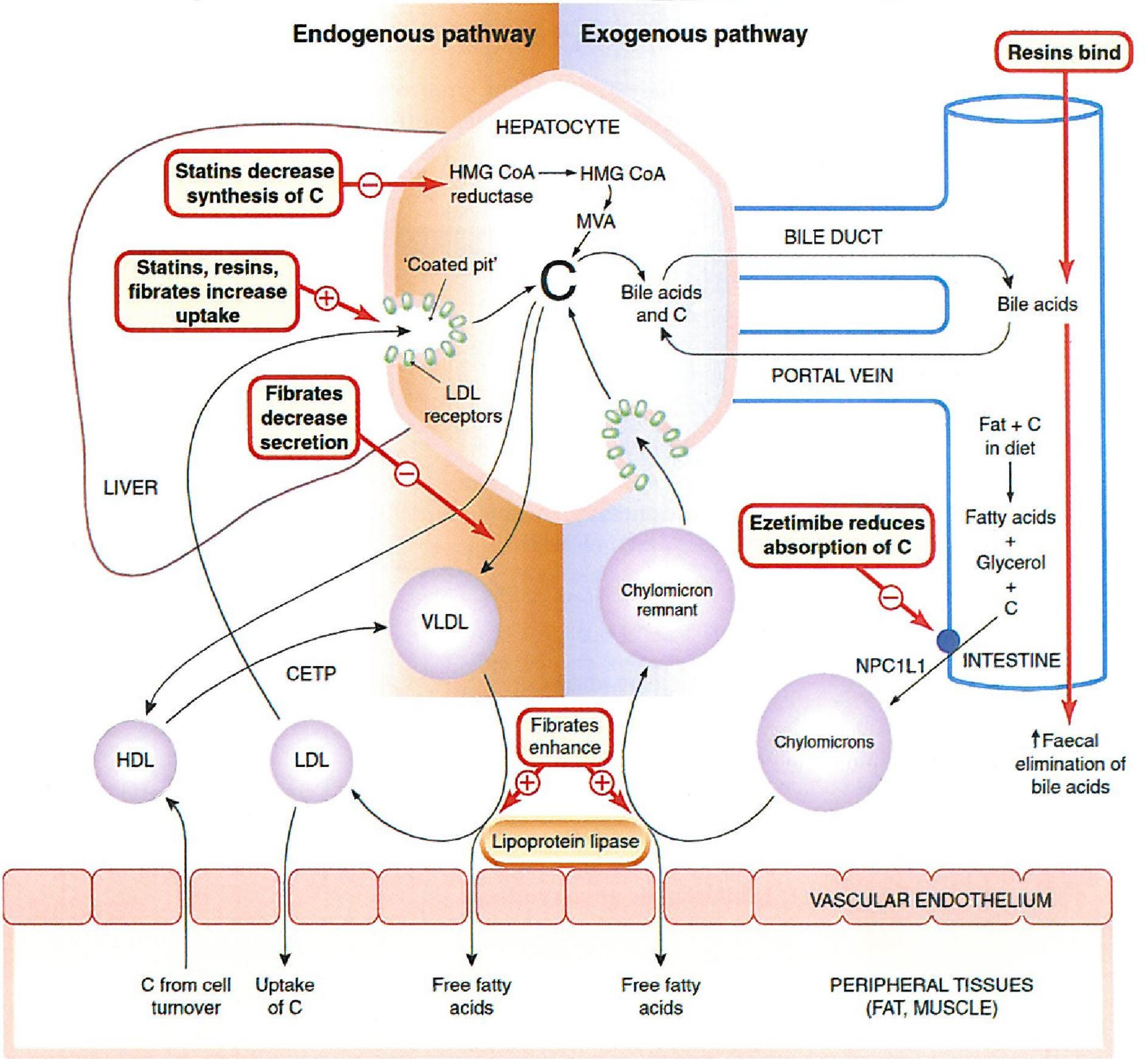
- ***Physical Activity***;

  - Regular aerobic physical activity 3-4 sessions a week, lasting on average 40 minutes per session and involving moderate to vigorous-intensity physical activity. This level of physical activity can reduce both LDL-C and non–HDL cholesterol.

- ***Reference***; 2013 American Heart Association/American College of Cardiology (AHA/ACC) Guideline on Lifestyle Management to Reduce Cardiovascular Risk.

Antihyperlipidemic Agents

- **Classes of Hyperlipidemia Medications**:
  - HMG-CoA Reductase Inhibitors (Statins).
  - Bile Acid Sequestrants (Resins).
  - Niacin (Nicotinic acid or Vitamin B3).
  - Fibric Acid Derivatives (Fibrates).
  - Cholesterol Absorption Inhibitors (Ezetimibe).
  - Omega-3 Fatty Acids.
  - Other Agents.


Endogenous pathway
Exogenous pathway
Resins bind
HEPATOCYTE
Statins decrease synthesis of C
HMG CoA reductase
HMG CoA
MVA
BILE DUCT
'Coated pit'
C
Statins, resins, fibrates increase uptake
Bile acids and C
Bile acids
LDL receptors
PORTAL VEIN
Fibrates decrease secretion
Fat + C in diet
LIVER
Fatty acids
+
Glycerol
+
C
Ezetimibe reduces absorption of C
Chylomicron remnant
VLDL
CETP
NPC1L1
INTESTINE
Chylomicrons
↑Faecal elimination of bile acids
HDL
LDL
Fibrates enhance
Lipoprotein lipase
VASCULAR ENDOTHELIUM
C from cell turnover
Uptake of C
Free fatty acids
Free fatty acids
PERIPHERAL TISSUES (FAT, MUSCLE)

- **C**; cholesterol.
- **CETP**; cholesteryl ester transport protein.
- **HDL**; high-density lipoprotein.
- **HMG-CoA reductase**; 3-hydroxy-3-methylglutaryl-coenzyme A reductase.
- **LDL**; low-density lipoprotein.
- **MVA**; Mevalonate.
- **NPC1L1**; a cholesterol transporter in the brush border of enterocytes.
- **VLDL**; very-low-density lipoprotein.

HMG-CoA Reductase Inhibitors (Statins)

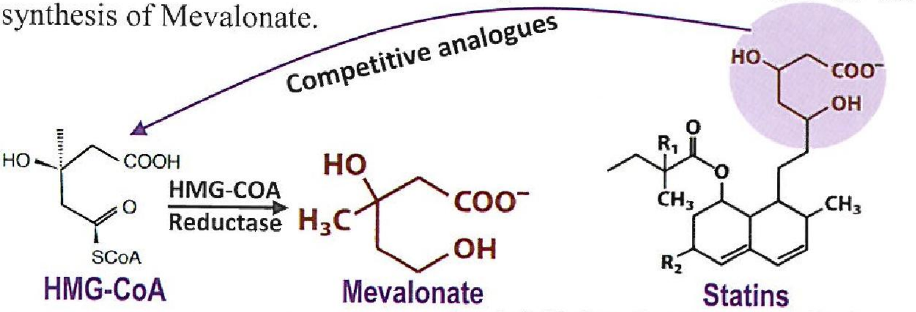
Atorvastatin (Lipitor®) **Pravastatin** (Lipostat®)	**Fluvastatin** (Lescol® XL) **Rosuvastatin** (Crestor®)	**Lovastatin** (Lipdip®) **Simvastatin** (Zocor®)
Pitavastatin (Lipostat®)		

- **Atorvastatin** [a-TOR-vah-stat-in], **Fluvastatin** [FLOO-vah-stat-in], **Lovastatin** [LOE-vah-stat-in], **pravastatin** [PRAH-vah-stat-in], **Rosuvastatin** [roe-SOO-va-stat-in], **Simvastatin** [sim-vah-STAT-in] and **Pitavastatin** [pit-AV-a-STAT-in] are ***competitive inhibitors*** of HMG CoA reductase.
- 3-Hydroxy-3-methylglutaryl coenzyme A (**HMG CoA**) **reductase inhibitors** (*commonly known as* **statins**) ***lower*** **elevated LDL-C**, resulting in a ***substantial reduction*** in **coronary events** and **death** from coronary heart disease (CHD).
- They are considered **first-line treatment** for **patients** with ***elevated risk*** of **atherosclerotic cardiovascular disease** (**ASCVD**).
- ***Therapeutic benefits*** include **plaque stabilization, improvement of coronary endothelial function, inhibition of platelet thrombus formation** and **anti-inflammatory activity.**
- The ***best-selling*** statin is **Atorvastatin**, in 2003 became the best-selling pharmaceutical in history.
- The manufacturer Pfizer (Lipitor®) reported sales of US$12.4 billion in 2008. Due to patent expirations, several statins are now available as less expensive generics.

Pharmaco Kinetics

	Bioavailability (%)	Half-life (h)	Metabolism	Prodrug	Solubility
Atorvastatin	12	14	3A4	No	Lipophilic
Fluvastatin	24	1	2C9	No	Hydrophilic
Lovastatin	<5	2–3	3A4	Yes	Lipophilic
Pravastatin	17	1.5–2	Non CYP	No	Hydrophilic
Rosuvastatin	20	20	2C19	No	Hydrophilic
Simvastatin	<5	2	3A4	Yes	Lipophilic
Pitavastatin	51	12	2C9, 2C8	Yes	Lipophilic

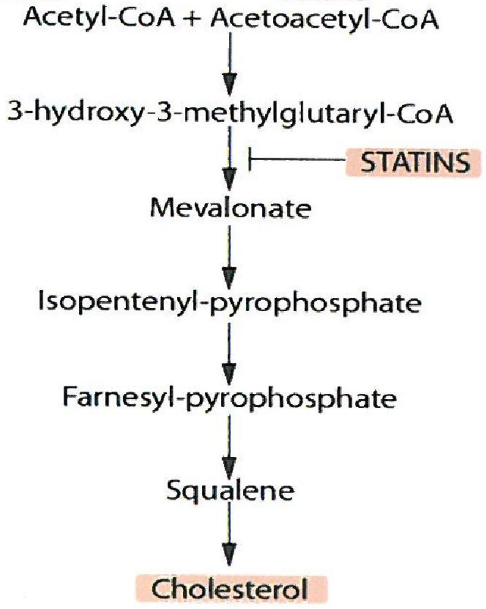
- The ***active forms*** of the **statins** are ***structural analogues*** of the **HMG-CoA intermediate** that is formed by HMG-CoA reductase in the synthesis of Mevalonate.


Competitive analogues
HO
COOH
O
SCoA
HMG-CoA
HMG-COA
Reductase
HO
H_3C
COO^-
OH
Mevalonate
HO
COO^-
OH
R_1
O
O
CH_3
CH_3
R_2
Statins

Mechanism OF Action

- These analogs (statins) cause partial inhibition of the enzyme. ***Result in***;

1) **Inhibition de novo synthesis of cholesterol** ⇨ deplete intracellular supply of cholesterol.
2) **Increase number of LDL receptors**, due to depletion of intracellular cholesterol ⇨ Promotes uptake of LDL from blood.
3) **Modest decreases in plasma triglycerides** and **small increases in HDL** also occur.


Acetyl-CoA + Acetoacetyl-CoA
3-hydroxy-3-methylglutaryl-CoA
STATINS
Mevalonate
Isopentenyl-pyrophosphate
Farnesyl-pyrophosphate
Squalene
Cholesterol

- **Pitavastatin**, **Rosuvastatin** and **Atorvastatin** are the ***most potent LDL cholesterol lowering statins***, ***followed by*** **Simvastatin** and **Pravastatin** ***then*** **Lovastatin** and **Fluvastatin**.

Therapeutic Uses

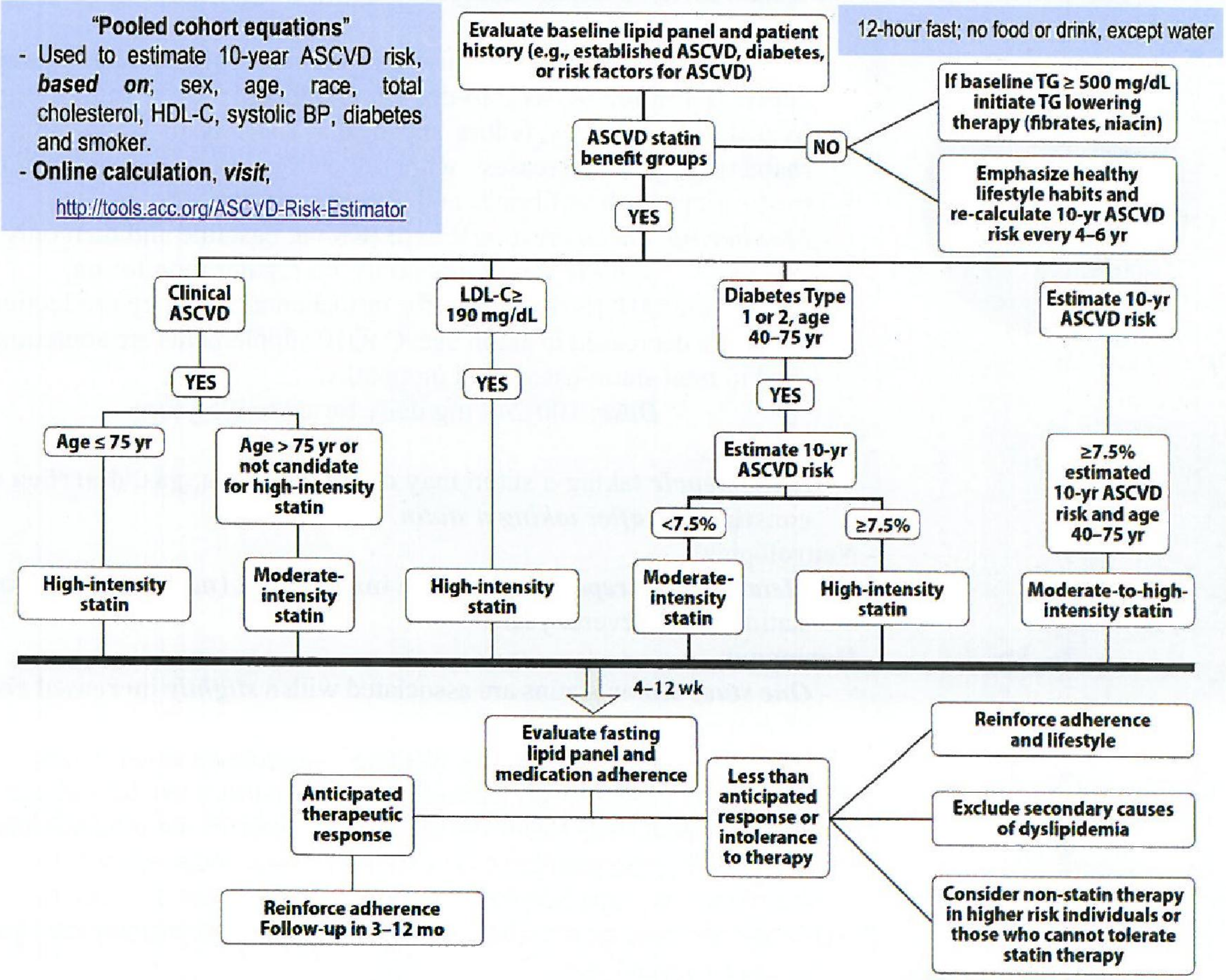
- **Statins** are useful alone or with resins, niacin or ezetimibe in **reducing levels of LDL.**
- Use in ***children*** is restricted to selected patients with **familial hypercholesterolemia** or **familial combined hyperlipidemia**.
- ***Women*** with **hyperlipidemia** who are **pregnant**, **lactating** or likely to **become pregnant** ***should not be*** given these agents.
- Because **cholesterol synthesis** ***occurs predominantly*** **at night**, **Statins** ***except*** **Atorvastatin** and **Rosuvastatin** ***should be given in the evening*** if a single daily dose is used.

Dose

- ***Intensity of Statin Doses***;

High Intensity	Moderate Intensity	Lower Intensity
When taken daily, will lower LDL an average of ≥ 50%	When taken daily, will lower LDL an average of 30% to < 50%	When taken daily, will lower LDL an average of < 30%
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg twice/d Pitavastatin 2-4 mg	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg

Statins Recommendation Therapy Algorithm



"Pooled cohort equations"
- Used to estimate 10-year ASCVD risk, ***based on***; sex, age, race, total cholesterol, HDL-C, systolic BP, diabetes and smoker.
- **Online calculation, *visit*;** http://tools.acc.org/ASCVD-Risk-Estimator

Evaluate baseline lipid panel and patient history (e.g., established ASCVD, diabetes, or risk factors for ASCVD)
12-hour fast; no food or drink, except water
ASCVD statin benefit groups
NO
If baseline TG ≥ 500 mg/dL initiate TG lowering therapy (fibrates, niacin)
Emphasize healthy lifestyle habits and re-calculate 10-yr ASCVD risk every 4–6 yr
YES
Clinical ASCVD
LDL-C≥ 190 mg/dL
Diabetes Type 1 or 2, age 40–75 yr
Estimate 10-yr ASCVD risk
YES
YES
YES
Age ≤ 75 yr
Age > 75 yr or not candidate for high-intensity statin
Estimate 10-yr ASCVD risk
<7.5%
≥7.5%
≥7.5% estimated 10-yr ASCVD risk and age 40–75 yr
High-intensity statin
Moderate-intensity statin
High-intensity statin
Moderate-intensity statin
High-intensity statin
Moderate-to-high-intensity statin
4–12 wk
Evaluate fasting lipid panel and medication adherence
Anticipated therapeutic response
Less than anticipated response or intolerance to therapy
Reinforce adherence and lifestyle
Exclude secondary causes of dyslipidemia
Consider non-statin therapy in higher risk individuals or those who cannot tolerate statin therapy
Reinforce adherence Follow-up in 3–12 mo

Reference; 2013 American Heart Association/American College of Cardiology (AHA/ACC) guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults.

Efficacy

- ***Reduce*** LDL-C by 24-60%.

Atorvastatin	Fluvastatin	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
55%	24%	34%	43%	34%	60%	41%

- ***Reduce*** TGs by 10-29%.

Atorvastatin	Fluvastatin	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
29%	10%	16%	18%	24%	18%	18%

- ***Raise*** HDL-C by 6-12%.

Atorvastatin	Fluvastatin	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
6%	8%	9%	8%	12%	8%	12%

- ***Reduce*** major coronary events.
- ***Reduce*** CHD mortality.
- ***Reduce*** coronary procedures (PCI or CABG).
- ***Reduce*** stroke by 17%.
- ***Reduce*** total mortality.

Side Effects

- **Hepatic**;
  - ***Elevated*** **liver enzymes** up to 3 times normal ***in*** **some patients**.
  - ***Monitoring*** **is usually needed** (liver function test); at 1–2 months, and then every 6–12 months (if stable).
  - **Statins** ***should be*** **discontinued** in patients whose liver enzymes activity is persistently elevated to ***more than*** **three times the upper limit of normal**.
- **Muscle**;
  - The ***most common statin side effect*** is **muscle pain** (10-15%).
  - ***Rare reactions*** statins can cause **myopathy** (inflammation of the muscles).
  - ***Very rarely***, statins can cause **life-threatening muscle damage** ***called*** **rhabdomyolysis** [rab-doe-mi-OL-ih-sis]; severe muscle pain, liver damage, kidney failure and death. The risk of statin-induced rhabdomyolysis increases with older age, use of interacting medications such as fibrates and hypothyroidism.
  - ***Monitoring***; check creatine kinase (CK) at baseline and then only if muscle symptoms occur; no regular monitoring.
  - **Coenzyme Q10** (is a cofactor for mitochondrial energy production) levels are decreased in statin use, CoQ10 supplements are sometimes used to treat statin-associated myopathy.
    - ***Dose***; 100-240 mg/daily for up to 2.5 years.
- **Digestive**;
  - ***Some people*** taking a statin may develop **nausea**, **gas**, **diarrhea** or **constipation** ***after taking a statin.***
- **Neurological**;
  - ***Meta-analysis reported*** **cognitive impairment** (**memory loss**) from statin use for several years.
- **Hormonal**;
  - ***One study show***; statins are associated with a ***slightly*** **increased risk of diabetes** (2-17%).

"FDA Warning" {Last Updated: January 31, 2014}

1) FDA has found that liver injury associated with statin use is rare but can occur.
2) Some drugs interact with statins in a way that increases the risk of muscle injury called myopathy, characterized by unexplained muscle weakness or pain. FDA is revising the drug label for Lovastatin to clarify the risk of myopathy.
3) FDA has been investigating reports of cognitive impairment (memory loss) from statin use for several years.
4) A small increased risk of raised blood sugar levels and the development of Type 2 diabetes have been reported with the use of statins.

Drug Interactions

- **Fibrates**: ***Increase*** **risk of myopathy** and **rhabdomyolysis** when coadministered with statins (**Gemfibrozil** ***greater than*** **Fenofibrate**).
- **Niacin**: Doses greater than 1 g/day ***increase*** **the risk of myopathy and rhabdomyolysis** when used concomitantly with statins; risk is lower than with fibrates; when statins and niacin are used together ⇨ monitor for muscle pain.
- **Amiodarone**, **Verapamil** and **Diltiazem** *also causes* an ***increased*** **risk of myopathy** when used with **Lovastatin** and **Simvastatin** (dose monitoring is needed).
- ***Inhibitors*** of CYP3A4 such as **Macrolide antibiotics**, **Cyclosporine**, **Ketoconazole** (and other azoles), ***some*** **HIV protease inhibitors**, **Tacrolimus** and **Nefazodone** may increase plasma levels of CYP3A4-dependent reductase inhibitors (**Lovastatin**, **Simvastatin**, and **Atorvastatin**).
- Plasma levels of **Lovastatin**, **Simvastatin** and **Atorvastatin** ***may be elevated*** in patients ingesting ***more than*** 1 liter of **grapefruit juice** daily.
- ***Inducers*** of CYP3A4 such as **Phenytoin**, **Griseofulvin**, **Barbiturates**, **Rifampin**, and **Thiazolidinediones** ***increase*** expression of CYP3A4 and can ***reduce the plasma concentrations*** of the 3A4-dependent reductase inhibitors (**Lovastatin**, **Simvastatin**, and **Atorvastatin**).
- ***Inhibitors of CYP2C9*** such as **Ketoconazole** (and other azoles), **Metronidazole**, **Sulfinpyrazone** and **Cimetidine** may increase plasma levels of **Fluvastatin** and **Rosuvastatin**.
- **Pravastatin** and **Rosuvastatin** appear to be the ***statins of choice for*** use with **verapamil**, **ketoconazole group**, **macrolides** and **cyclosporine**.

Contra indication

- Active liver disease, unexplained persistent elevations in liver enzymes.
- Pregnancy (FDA Pregnancy Category X).
- Lactating women (Nursing mothers)

Bile Acid Sequestrants (Resins)

Cholestyramine (Questran®)	**Colesevelam** (Cholestagel®)	**Colestipol** (Colestid®)

- **Cholestyramine** [koe-LES-tir-a-meen], **Colestipol** [koe-LES-tih-pole] and **Colesevelam** [koh-le-SEV-e-lam] are ***anion-exchange resins*** that bind negatively charged bile acids and bile salts in the small intestine.

Pharmaco Kinetics

- Bile acid sequestrants are ***insoluble*** **in water** and have large Mwt.
- After oral administration, they are **not absorbed** and **not metabolically altered** ***by the*** **intestine**.
- They are ***totally*** **excreted in feces**.

Mechanism OF Action

- Bile salts is manufactured and secreted by the liver and stored in the gallbladder responsible for emulsifies fat and lipids to facilitate absorption in the intestine.
- **Bile acid sequestrants** are anion-exchange resins that **bind** ***negatively charged*** with **bile acids** in the small intestine, resin/bile acid complex is excreted in the feces ⇨ ***lowering*** **bile acid** concentration ⇨ This causes hepatocytes to ***increase conversion*** of **cholesterol** to **bile acids**.
- ***Consequently***;
  - ***Decrease*** **intracellular cholesterol concentrations**.
  - ***Increase*** **hepatic uptake of LDL-C**.
  - ***Decrease*** in **plasma LDL-C**.

Efficacy

- ***Reduce*** LDL-C by 15-26%.
- ***Raise*** HDL-C by 3-6%.
- May ***increase*** TG concentrations.
- ***Reduce*** major coronary events.
- ***Reduce*** CHD mortality.

Therapeutic Uses

- **Resins** are also ***used*** in **combination** with other drugs to achieve further hypocholesterolemic effect in **patients with primary hypercholesterolemia** and ***treating*** **type IIA** and **type IIB hyperlipidemias.**
- **Cholestyramine** can also **relieve pruritus** caused by accumulation of bile acids in patients with biliary stasis.
- ***Because*** the **resins** ***bind*** **digitalis glycosides**, they may be **useful in digitalis toxicity**.
- **Colesevelam** is also ***indicated*** for **type 2 diabetes** due to its glucose-lowering effects.

Dose

- Resins should be taken in two or three doses with meals.
- **Cholestyramine** are available as granular preparations;
  - ***Initial dose***; 4 g orally once or twice a day.
  - ***Gradual increase*** to ***maintenance dose***; 20 g/d is recommended.
  - ***Total dosages*** of 30–32 g/d may be needed for maximum effect.
  - The usual ***dosage for a child*** is 10-20 g/d.
  - Granular are mixed with juice/water & allowed to hydrate for 1 min.
- **Colestipol** are available as granular and tablet (1 grams) preparations;
  - ***Initial dose***: 5 g of the granules orally once or twice daily (in liquid) or 2 tablets (2 grams) orally once or twice daily.
  - ***Maintenance dose***: Doses may be titrated in 2 or 5 g daily increments every 1 to 2 months.
- **Colesevelam** are available as tablets (625 mg) and suspension (1875 mg and 3750 mg);
  - 1875 mg (3 tablets) orally twice a day or 3750 mg (6 tablets) orally once a day. ***Oral suspension*** is one 3.75 gram once daily or one 1.875 gram twice daily.

Side Effects

- **GI disturbances**;
  - Such as; **Constipation**, **nausea** and **flatulence**.
  - **Colesevelam** has ***fewer*** **GI side effects.**
  - Usually ***relieved by*** **increasing dietary fiber** or **mixing psyllium seed** with the resin.
- **Malabsorption of fat-soluble vitamins** (A, D, E and K) ***may occur***;
  - **Colesevelam** has ***no*** or ***fewer*** effects.
  - **Usually *not* used with pregnant** women ***due to*** vitamin deficiencies that may affect the fetus.

Drug Interactions

- **Absorption** of ***certain*** **drugs**, including those with neutral or cationic charge as well as anions, ***may be*** **impaired** by the **resins**. ***These include***;
  - **Digitalis glycosides**, **Thiazides**, **Warfarin**, **Tetracycline**, **Thyroxine**, **Iron salts**, **Pravastatin**, **Fluvastatin**, **Ezetimibe**, **Folic acid**, **Phenylbutazone**, **Aspirin**, and **Ascorbic acid**, ***among others***.
  - ***In general***, additional medication (***except*** **Niacin**) ***should be*** given at least **1 to 2 hours before *or* 4 to 6 hours after**, the bile acid-binding resins.
  - **Colesevelam** does ***not bind*** **Digoxin**, **Warfarin** or **Statins**.

- ***Contraindications***; These agents may raise triglyceride levels and are contraindicated in **patients with significant hypertriglyceridemia** (≥400 mg/dL).

Niacin (Nicotinic Acid or Vitamin B3)

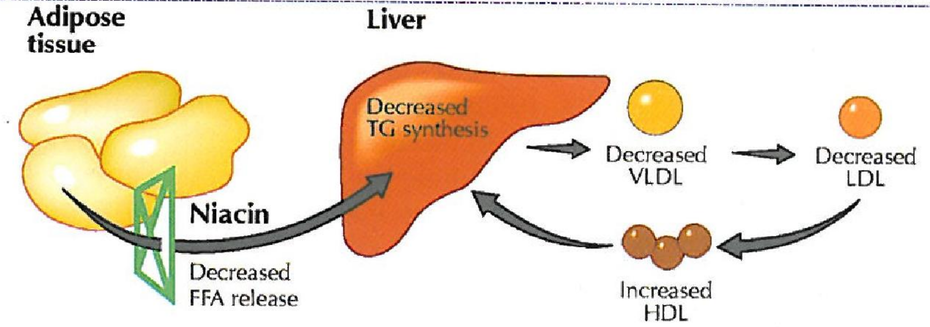
Niacin (Niaspan®)

- **Niacin** or **Nicotinic acid** [NYE-uh-sin] [NIK-oh-TIN-ik AS-id] (not Niacinamide) is a **Vitamin B3**, it is primarily ***used*** to treat **hypercholesterolemia** and **pellagra** (niacin deficiency).
- It occurs naturally in plants and animals, and is also added to many foods as a vitamin supplement. It is also present in many multiple vitamins and nutritional supplements.

Pharmaco Kinetics

- **Niacin** is ***administered* orally**.
- It is ***converted*** in the body to **Nicotinamide**, which is ***incorporated into*** the cofactor nicotinamide adenine dinucleotide (**NAD$^+$**)
- *N.B*; **Nicotinamide *alone* does not *decrease* plasma lipid levels.**
- **Niacin** and its **other derivative metabolites** are ***excreted*** in the **urine**.

Mechanism OF Action



- ***At 1 gm dose***;
  - **Niacin *strongly inhibits* lipolysis** in adipose tissue, thereby ***reducing*** production of **free fatty acids.**
  - The liver normally uses circulating free fatty acids as a major precursor for triglyceride synthesis.
  - ***Reduced*** liver **triglyceride** levels;
    - ***Decrease*** hepatic **VLDL** production.
    - ***Reduces* LDL-C** plasma concentrations.

Therapeutic Uses

- **Niacin** often ***used*** in **combination** with a **Resin** or **Statins**, it is normalizes LDL in most ***patients*** with **familial hypercholesterolemia** and other forms of **hypercholesterolemia**.
  - ***Dose***;
    - ***Intermediate Release***; *Initial*: 100 mg orally 3 times a day, with or after meals. *Maintenance*: 1 to 2 g orally 3 times a day, with or after meals (Max. dose 6 g/day).
    - ***Extended Release*** (Niaspan®); *Initial*: 500 mg orally once a day at bedtime. *Maximum* dose is 2 g/day.
    - ***Sustained Release*** (Slo-Niacin®); *Initial*: 250-750 mg orally once a day morning or evening.
- ***Used*** in niacin deficiency (**pellagra**).
- **Niacin** or **Nicotinamide *used topically*** for many **skin problems**.

"Skin Benefits of Niacin and Niacin Derivatives"

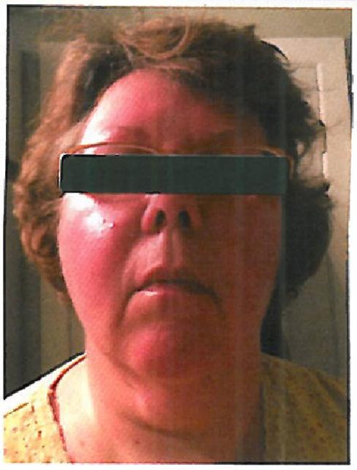
- **Acne**; Topical 4% nicotinamide gel was as effective as 1% clindamycin gel in the treatment of moderate inflammatory acne vulgaris.
- **Lip Plumper**; Niacin is applied topically as a lip plumper, due to its vasodilation effect. The vasodilator effect on lips are slightly swollen and redder, making them appear "full-blooming" which is typically desired.
- **Moisturizing Effects**; Nicotinamide 2% cream more effective than petrolatum, the same ingredient in Vaseline, at boosting hydration levels in the patient's dry skin.
- **Rosacea Improvement**; Nicotinamide moisturizer provided substantial improvements in rosacea symptoms.
- **Possible Skin Cancer Prevention**; Oral (500 mg) nicotinamide prevent the progression of premalignant actinic keratoses to malignant squamous cell cancers.
- **Reduce Wrinkles**; Topical nicotinamide provided reductions in fine lines and wrinkles.
- **Skin Whitening**; Topical nicotinamide provided reductions hyperpigmented spots.

Efficacy

- ***Lowers*** LDL-C by 15-26%.
- ***Lowers*** TG by 20-50%.
- ***Raises*** HDL-C by 15-26%.
- ***Reduces*** major coronary events.
- ***Lowers*** lipoprotein (A).

Side Effects

1) **Niacin Flush (Facial Flushing)**;



   - The most common side effects of niacin are an ***intense* cutaneous flush** (accompanied by an uncomfortable feeling of warmth) and **pruritus**, ***due to prostaglandin mediated vasodilation effect.***
   - Symptoms occurred in up to **78% of patients** and ***usually resolved*** **after 2 weeks** of continued therapy.
   - Flushing usually ***lasts for*** about **15** to **30 minutes**.
   - **Flushing** can be ***minimized by***;
     1) Taking **Aspirin** 325 mg or **Ibuprofen** 200 mg 30-60 minutes before niacin.
     2) Use of an extended release form of the drug.
     3) Gradual dosage titration (over 2 to 3 months).
     4) Administering the dose during or within 30 min. after meals.
     5) Taking Niacin at bedtime with food and avoiding hot beverages, spicy foods and hot showers around the time of administration.

2) **Upper GI Distress**;
   - Some patients experience **nausea** and **dyspepsia (indigestion)**.

3) **Hepatic**;
   - ***Reversible elevations*** in **liver enzymes** up to twice normal may occur, usually not associated with liver toxicity.
   - ***Monitor*** liver enzymes level, every 6-12 weeks and then yearly.

4) **Metabolic**;
   - **Hyperuricemia**; ***due to*** niacin inhibits tubular secretion of uric acid, more common in men. **Allopurinol** can be given with niacin if needed.
   - Carbohydrate tolerance (**hyperglycemia**) may be moderately impaired, especially in obese patients, but this is usually reversible.

5) **Other**;
   - ***Rarely***, niacin is associated with **arrhythmias**.

- ***Contraindications***; **Liver disease**, **severe gout** and **active peptic ulcer**.
- ***Pregnancy***; Category C by the FDA, it has been associated with birth defects in laboratory animals.
- ***Lactating Women***; Niacin is excreted in human milk, may cause serious adverse reactions in infants.

Fibric Acid Derivatives (Fibrates)

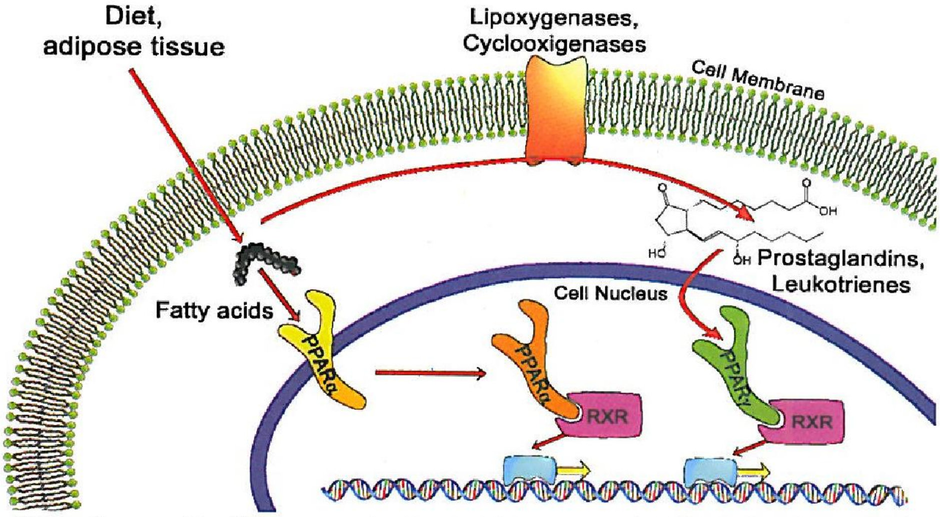
Fenofibrate (Lipanthyl®)	**Gemfibrozil** (Lopid®)

- The ***most common fibrates*** used are **Fenofibrate** [fen-oh-FIH-brate] and **Gemfibrozil** [jem-FI-broh-zill]. Another fibrate such as, **Bezafibrate**, is not yet available in the USA.

Pharmaco Kinetics

- **Fenofibrate**;
  - It is a ***pro-drug*** of the active chemical moiety **Fenofibric acid**.
  - ***Completely*** **absorbed** after oral administration, **distribute *widely*** and ***bound*** to **plasma proteins.**
  - ***Plasma half-life*** is **20 hours**.
  - **60%** is ***excreted*** in the **urine** as the glucuronide and **~ 25% *in* feces.**
  - Lipanthyl® **Supra**; is a film-coated tablet of ***micronized*** **Fenofibrate** and is **supra-bioavailable** (larger bioavailability).
- **Gemfibrozil**;
  - ***Completely*** **absorbed** after oral administration, **distribute *widely*** and ***bound*** to **plasma proteins.**
  - ***Plasma half-life*** is **1.5 hours**.
  - **70%** is ***excreted*** in the **urine** as the glucuronide.

Mechanism OF Action



- **Peroxisome Proliferator–Activated Receptors (PPARs)** are members of the nuclear receptor supergene family that ***regulates lipid metabolism.*** Upon binding to their natural ligands (fatty acids or eicosanoids) PPARs are activated.
- **Fibrates** function primarily as ***ligands*** for the nuclear transcription receptor **(PPAR-α)** ⇨ ***activate*** **PPAR-α** ⇨ ***decreased*** **triglyceride** concentrations **by *increasing*** the *expression* of **lipoprotein lipase** and ***decreasing*** **Apo-CII concentration** (**Fenofibrate** is ***more effective*** than **Gemfibrozil** in ***lowering*** **triglyceride levels**).
- **Fibrates** also ***increase*** the level of **HDL-C** by ***increasing*** the *expression* of **Apo-A**.

Efficacy

- ***Lower*** LDL-C by 5-20% (with normal TGs).
- May ***raise*** LDL-C by 45% (with very high TGs).
- ***Lower*** TG by 30-55%.
- ***Raise*** HDL-C by 18-22%.
- ***Reduce*** progression of coronary lesions.

Therapeutic Uses

- They are ***useful*** in ***severe*** **hypertriglyceridemia**.
- They are ***useful*** in **hypertriglyceridemia** *in which* **VLDL *predominate*.**
- They are ***useful*** in **dysbetalipoproteinemia (Type III hyperlipidemia)**.
- They also may be of ***benefit*** in ***treating*** the **hypertriglyceridemia** that ***results from treatment with*** **viral protease inhibitors**.

Dose

- **Fenofibrate**;
  - Fenofibrate is available in several formulations with several dose range and is sold under several brand names.
  - The initial dose of tablets ranges from 40- 160 mg per day.
- **Gemfibrozil**;
  - 600 mg orally twice a day, 30 minutes before meal.

Side Effects

- **Mild GI disturbances**;
  - Mild GI disturbances are the ***most common***.
- **Gallstones**;
  - Gallstones ***may occur*** due to ↑ biliary cholesterol excretion.
- **Myositis**;
  - **Muscle inflammation** and **pain *can occur***.
  - Patients with **renal insufficiency** may be at ***risk***.
  - **Myopathy** and **rhabdomyolysis** have been reported in ***patients taking* Gemfibrozil** and **Statins *together***.
  - The use of **Gemfibrozil** is ***contraindicated*** with **Simvastatin**.
  - **Fenofibrate** is the fibrate of ***choice for*** use in **combination with a Statins**.
- **Hepatic**; ***Elevated* liver enzymes** may occur ***in* some patients** (monitor liver enzymes every 3 months during first year).

- ***Pregnancy***; category C.
- Both fibrates may ***increase*** the effects of **Warfarin**.
- ***Contraindications***: Severe renal or hepatic disease and patients with preexisting gallbladder disease.

Cholesterol Absorption Inhibitors

Ezetimibe (Ezetrol®)

- **Ezetimibe** [eh-ZEH-teh-mib] is the first member of a group of drugs that inhibit intestinal absorption of cholesterol.

Pharmaco Kinetics

- ***Absorption***; it is absorbed and extensively conjugated to active glucuronide (Ezetimibe-glucuronide).
- ***Protein binding***; Ezetimibe-glucuronide are highly bound (>90%) to plasma proteins.
- ***Peak***; plasma peak attained within 12-14 hours;
  - Plasma concentrations are substantially ***increased*** when it is administered with **Fibrates** and ***reduced*** when it is given with **Cholestyramine**.
- ***Half-life***; 22 hours.
- ***Excretion***; approximately 80% of the drug is excreted in feces.

Mechanism OF Action

- It is a ***selective inhibitor*** of **intestinal absorption** of **cholesterol** and **phytosterols** (plant sterols), leading to a ***decrease*** in the **delivery** of **intestinal cholesterol** *to the* **liver**.
- ***Reduction*** of **hepatic cholesterol stores**, *leading to* an ***increase*** in **clearance of cholesterol** from the blood.
- It is **effective** even in the **absence of dietary cholesterol** *because* it ***inhibits* reabsorption** of **cholesterol excreted in** the **bile**.

Efficacy

- ***Lowers*** LDL-C by 18-20%.
- May ***raise*** HDL-C by 1-5%.
- ***Lowers*** TG by 5-10%.

Therapeutic Uses

- **Ezetimibe** is *synergistic* with **Statins**, ***so*** it is often ***used*** as an;
    - **Adjunct to statin therapy**.
    - **Statin-intolerant patients**.
- *Dose*;
    - Dosage range of 5-20 mg/d.
    - Usually single daily dose; 10 mg/d.

- ***Recent data***; suggest that **Ezetimibe** combination with **Simvastatin** is ***superior than*** **Simvastatin** ***alone*** in ***reducing*** **cardiovascular events**.
- ***Side effects***; headache and rash (**rare**).
- ***Drug interaction***; There are ***no significant*** interactions with **Warfarin** or **Digoxin**.

➢ Summary of Antihyperlipidemic Drug Efficacy:-

	Effect on LDL	Effect on HDL	Effect on TGs
Statins	↓↓↓↓	↑↑	↓↓
Fibrates	↓	↑↑↑	↓↓↓↓
Niacin	↓↓	↑↑↑↑	↓↓↓
Bile Acid Sequestrants (Resins)	↓↓↓	↑	↑
Cholesterol Absorption Inhibitors	↓	↑	↓

➢ Combination Drug Therapy:-

- **Advantage of combination drug therapy, *is useful*** When LDL and VLDL levels are both elevated initially or not normalized with a single agent.

1) **Fibrates + Resins**; ✓
    - This combination is sometimes useful in treating patients with familial combined hyperlipidemia who are intolerant to niacin or statins.
    - It may increase the risk of cholelithiasis (gallstones).
2) **Statins + Resins**; ✓
    - This synergistic combination is be very useful in lowering LDL-C levels.
    - Statins *should be* given 1 hour before or 4 hours after the resin absorption.
3) **Niacin + Resins**; ✓
    - This combination effectively controls VLDL levels during resin therapy.
    - The drugs may be taken together, because niacin does not bind to the resins.
4) **Niacin + Statins**; ✓✓
    - This regimen is more effective than either agent alone in in lowering LDL-C levels and increasing HDL-C level.
    - Risk of myopathy and hepatitis.
    - **Niacin + Lovastatin**; appears relatively safe and well tolerated with myopathy and hepatitis risk.
5) **Statins + Ezetimibe**; ✓✓✓
    - This combination is highly synergistic in lowering LDL-C levels.
    - **Simvastatin + Ezetimibe**; This combination very useful in lowering **cardiovascular events**.
6) **Statins + Fenofibrate**; !
    - This combination is appears to be effective in conditions involving elevations of both LDL and VLDL, but risk of liver and muscle toxicity is indicated.
    - **Fenofibrate + Rosuvastatin** appears to be well tolerated.
    - **Statins + Gemfibrozil**; This combination is contraindicated due to risk of severe myopathy and rhabdomyolysis.

Omega-3 Fatty Acids

Omega-3 Fatty Acids (Lovaza®) (Vascepa®) (Epanova®)

- **Omega-3 Fatty Acids**; (ω-3 fatty acids) are **essential fatty acids, polyunsaturated fatty acids (PUFAs)** with a double bond (C=C) at the third carbon atom from the end of the carbon chain.
- **Essential fatty acids** ***inhibit*** **VLDL** and **triglyceride** ***synthesis*** in the liver (unknown mechanism).
- The ***three types*** of **omega-3 fatty acids** involved ***in*** **human** physiology are **α-linolenic acid** (**ALA**) (found in plant oils), **Eicosapentaenoic acid** (**EPA**), and **Docosahexaenoic acid** (**DHA**) (both commonly found in marine oils).
- *Efficacy* (**DHA** and **EPA**) Lovaza®;
    - ***Lowers*** TG by 26-45%.
    - May ***raise*** in LDL-C to 45% when TG concentrations are very high.
        - **Icosapent** [eye-KOE-sa-pent] **ethyl** (Vascepa®); is a form of EPA, unlike other fish oil supplements, does not significantly raise LDL-C and lowers TG by 33%.
    - ***Raises*** HDL-C by 11-14%.
- *Uses*; ***treat*** **hypertriglyceridemia** as an **adjunct** ***to*** **diet** in **adults** with **TG conc.** of **≥ 500 mg/dL**.
- *Dose*;
    - **DHA** and **EPA** (Lovaza®); 4 g/day as a single dose or in two divided doses.
    - **Icosapent ethyl** (Vascepa®); 2 g twice daily with food.
- *Side effects*;
    - **GI effects** (abdominal pain, nausea and diarrhea) and **fishy aftertaste**.
    - **Risk of bleeding** especially in patients who are taking anticoagulant or antiplatelet drugs (***due to*** it inhibit platelet aggregation).
- *N.B*;
    - **Omega-6 fatty acids**; are essential fatty acids (polyunsaturated fat).
    - **Omega-9 fatty acids**; are monounsaturated fats.
    - **Omega-3-6-9 fatty acids** play specific roles in overall health;
        - ***Prevent***; coronary heart disease, stroke and diabetes.
        - ***Promote***; healthy nerve activity and cell development
        - ***Maintain*** a healthy immune system.
- **Omega-3-Carboxylic Acid** (Epanova®);
    - *Efficacy*;
        - ***Lowers*** TG by 30%.
        - May ***raise*** HDL-C by 5%.
        - May ***raise*** LDL-C by 25%.
    - *Uses*; ***treat*** **hypertriglyceridemia** as an **adjunct** ***to*** **diet** with **TG conc.** of **≥ 500 mg/dL**.
    - *Side effects*: ***Diarrhea***.
    - *Dose*; 2 g or 4 g once daily.

Other Agents

Lomitapide (Juxtapid®)

- **Lomitapide** [loe-MI-ta-pide] is ***selective* microsomal triglyceride transfer protein (MTP or MTTP) *inhibitor***, which is necessary for VLDL assembly and secretion in the liver.
- ***Efficacy***; ***lowers*** LDL-C by about 40%.
- ***Uses***; approved by the FDA (2012) to as "an adjunct to a low-fat diet and other lipid-lowering treatments in patients with **homozygous familial hypercholesterolemia (HoFH)**; HoFH is rare medical condition, harder to treat due to the LDL receptors are minimally functional.
- ***Dose***; *initial adult dose* is 5 mg daily.
- ***Most common side effects***: ***elevated* liver enzymes** and **GI symptoms**.
- ***FDA warning***; ***risk*** of **hepatotoxicity**.

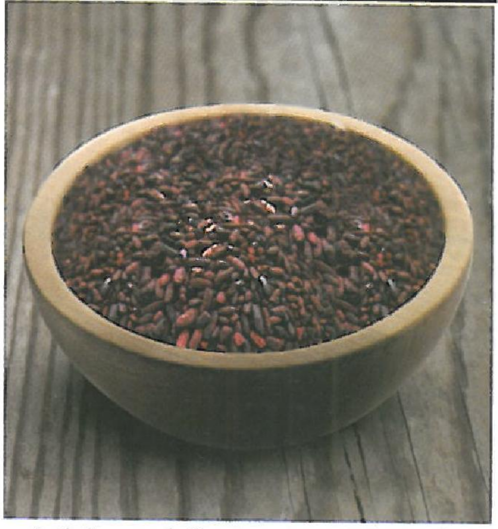
Mipomersen (Kynamro®)

- **Mipomersen** [MYE-poe-mer-sen] is an antisense therapeutic that targets the messenger RNA for apolipoprotein B.
- ***Efficacy***; ***lowers*** LDL-C by about 25%.
- ***Uses***; approved by the FDA (2013) to ***treat* homozygous familial hypercholesterolemia (HoFH)**.
- ***Dose***; 200 mg SC once weekly.
- ***Most common side effects***; ***elevated* liver enzymes** and **flu-like symptoms**.
- ***FDA warning***; ***risk*** of **hepatotoxicity**.

Torcetrapib | Anacetrapib | Dalcetrapib

- **Torcetrapib**, **Anacetrapib** and **Dalcetrapib** are a ***cholesteryl ester transfer protein* (CETP) *inhibitors***, they are causes markedly increased HDL and reduced LDL.
- **Torcetrapib** is the first drug in this class it was ***withdrawn from* clinical trials** because it increased cardiovascular events and deaths.
- **Anacetrapib** and **Dalcetrapib** are analogs currently in clinical trials.

Red Yeast Rice (Cholestin®) (Statosan®)



- **Red Yeast Rice (RYR)** is ***made from*** yeast (*Monascus purpureus*) grown on rice. It is a bright reddish purple colour.
- It is a dietary staple in some Asian countries (**Japanese**), going back to 300 BC.
- RYR contains several compounds known as **Monacolins**, which ***block* cholesterol production**.
- ***One of these***, **Monacolin K**, has the same structure as the drugs **Lovastatin**.
- ***It also contains* Sterols**, **Isoflavones**, and **Monounsaturated Fatty Acids**.
- Studies suggest that RYR may lead to a 10-33% ***reduction*** in **LDL-C** and may ***increase*** levels of **HDL-C**.
- RYR extract has been sold in supplements to ***lower* cholesterol** and may have benefits in **diabetes** and **CHD**.
- ***Dose***; *for high cholesterol*; 1,200-2,400 mg of red yeast powder 1-2 times daily for up to 12 weeks.
- ***Side effects***: ***elevated* liver enzymes** and **GI symptoms**.

Garlic (Tomex®)

- The results of research on garlic have been **mixed**, but it ***may help*** lower blood pressure, reduce blood cholesterol levels, and slow the progress of atherosclerosis. Some evidence suggests that taking garlic supplements can slightly lower blood cholesterol levels.
- For example, studies have shown positive **effects** for ***short-term*** use of one to three months. ***However***, National Center for Complementary and Alternative Medicine (NCCAM) study on the safety and effectiveness of three garlic preparations found ***no long-term effect*** on lowering blood cholesterol levels.

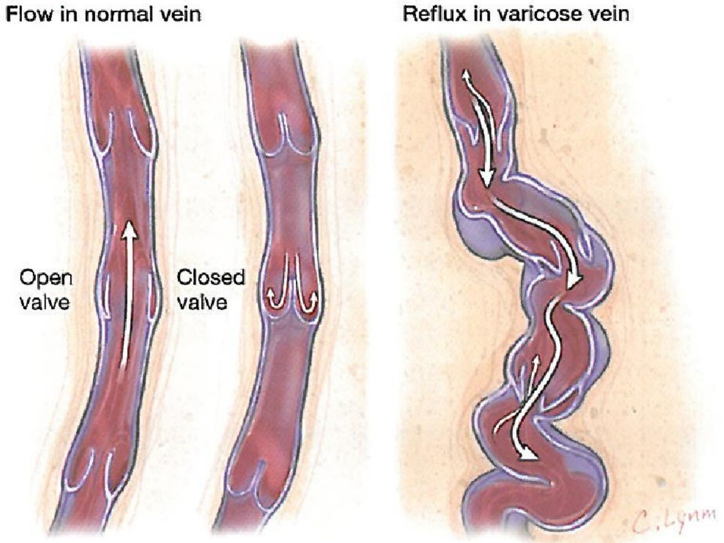
Venous Insufficiency

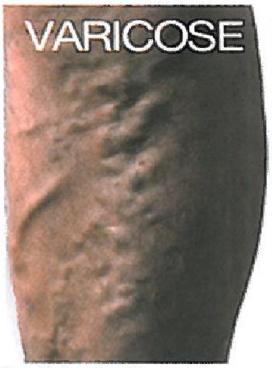
- **Venous Insufficiency**; is a condition in which the **blood flow *through*** the **veins** is ***impaired***.
- **Chronic venous insufficiency** (**CVI**) is a chronic condition of venous insufficiency.
- Venous insufficiency can be ***caused by*** a number of disorders of the veins, *particularly* **deep vein thrombosis (DVT)** or **varicose veins**.
- **In healthy veins**; ***continuous*** **blood flow** from the limbs back toward the heart.
- **Valves** within the veins of the legs that ***prevent*** **the backflow of blood**.
- **Venous insufficiency** occurs when ***forward*** **blood flow** through the veins is **obstructed**, as in the case of a *blood clot* or if there is *backward leakage of blood flow* through damaged valves.

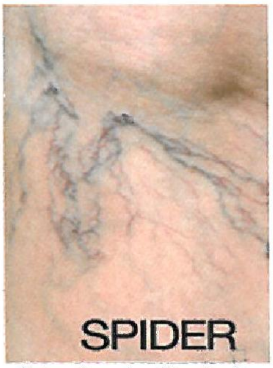
Varicose Veins (VVs)

Overview:-

- **Varicose veins** (or **spider veins**; small veins); are veins that have become enlarged and twisted with reversed blood flow.
- They are **visible *surface manifestations***.
- **Prevalence**; 5-30% in the adult population, with a female to male predominance of 3 to 1.
- ***Mild forms*** of venous insufficiency are merely uncomfortable, annoying or cosmetically disfiguring, *but* ***severe venous disease*** can produce serious systemic consequences and can lead to loss of life or limb.



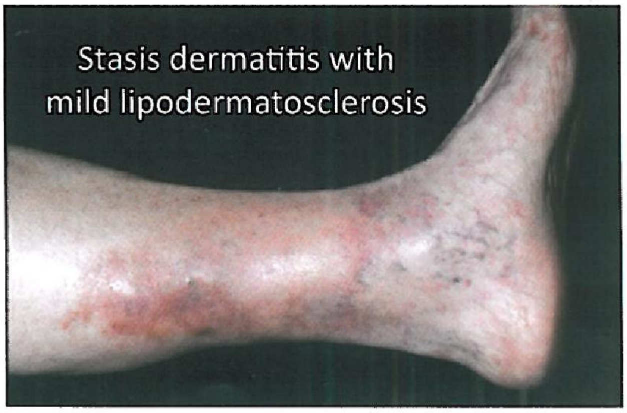




Signs and Symptoms:-

Symptoms are vary according to their size and extent and *include*;

- **Aching** (painful) and **Heavy Legs**; often worse at night and after exercise.
- **Spider Veins** (or **telangiectasia**).
- **Ankle Swelling**; especially in evening.
- **Brownish-yellow** skin **discoloration**.
- **Stasis Dermatitis** (**venous eczema**); redness, dryness and itchiness of areas of skin, due to the buildup of pressure and toxins in the leg.
- **Lipodermatosclerosis**; in some people the skin above the ankle may **shrink** ***because*** the fat underneath the skin becomes hard.
- **Cramping**; especially when sudden move as standing up.
- **Minor Injuries**; ***due to*** **itching** and may take a long time to heal.
- **Atrophie Blanche**; **Whitened *irregular scar-like patches*** can appear at the ankles.



Stasis dermatitis with mild lipodermatosclerosis

➢ Complications:-

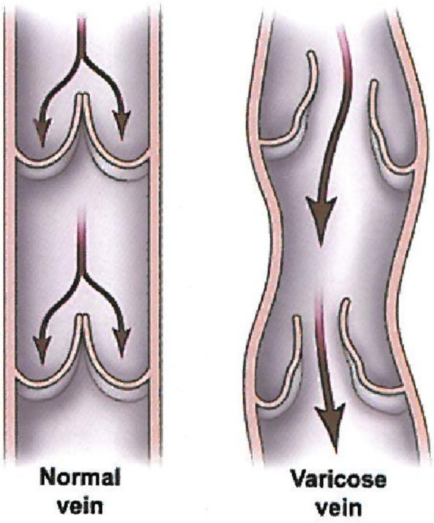
- ***Due to*** the ***long term*** **poor circulation** through the affected limb.
  - **Pain**, **tenderness**, **heaviness**, **inability to walk** **or** **stand *for* long period**.
  - **Stasis dermatitis**; continuous itching lead to injury.
  - **Venous ulcers**; especially near the ankle.
  - **Carcinoma**; can occur, especially in longstanding venous ulcers.
  - **Acute fat necrosis**; can occur, especially at the ankle of overweight patients.

➢ Risk Factors:-

- **Age**; the risk of varicose veins increases with age.
- **Sex**; women are more likely to develop the condition, due to hormonal changes during pregnancy, pre-menstruation or menopause.
- **Pregnancy**; due to increases the volume of blood in the body.
- **Obesity**; overweight puts added pressure on the veins.
- **Standing** or **sitting *for* long periods**.
- **Family history**.

➢ Pathophysiology:-

- The venous system acts as both a reservoir and a conduit in the return of blood to the heart and lungs for oxygenation and re-circulation.
- Veins are thin-walled and lack the muscular walls of arteries. Therefore, veins require assistance in blood return. This is provided by valves and muscle pumps. When one of these factors is not functioning properly, venous hypertension and insufficiency can ensue, possibly leading to varicose veins.
- A normal vein wall has 3 smooth muscle layers that all help to maintain vein tone. Varicose veins demonstrate marked proliferation of collagen matrix as well as decreased elastin, leading to distortion and disruption of muscle fibre layers.



➢ Diagnosis:-

- **History**; a ***previous history of*** DVTs or thrombophlebitis, thrombophilia, current medications (*especially* oral contraceptives), smoking, previous and present pregnancies and a family history of varicose veins.
- **Physical Examination**; ***involves*** inspection and palpation of the lower limbs while the patient is standing. The legs are observed for dilated veins, spider veins or telangiectasia, edema that is pitting or non-pitting, indurations, hyperpigmentation, lipodermatosclerosis, dermatitis, atrophie blanche, eczema, active or healed ulcerations, and any other skin discolorations.
- **Screening**;
  - **Duplex ultrasound scanning**; is now the gold standard and first diagnostic test for assessing the lower limbs in patients with suspected varicose veins.
  - **Magnetic resonance venography** is another test performed when the Duplex scan test is unclear. This test can even look in the deep veins.

➢ **CEAP Classification:** It has been developed to allow uniform diagnosis.

Clinical*

C_0 - No clinical signs
C_1 - Small varicose veins
C_2 - Large varicose veins
C_3 - Edema
C_4 - Skin changes without ulceration
C_5 - Skin changes with healed ulceration
C_6 - Skin changes with active ulceration

Etiology*

E_C - Congenital
E_P - Primary
E_S - Secondary
(usually due to prior DVT)

Anatomy*

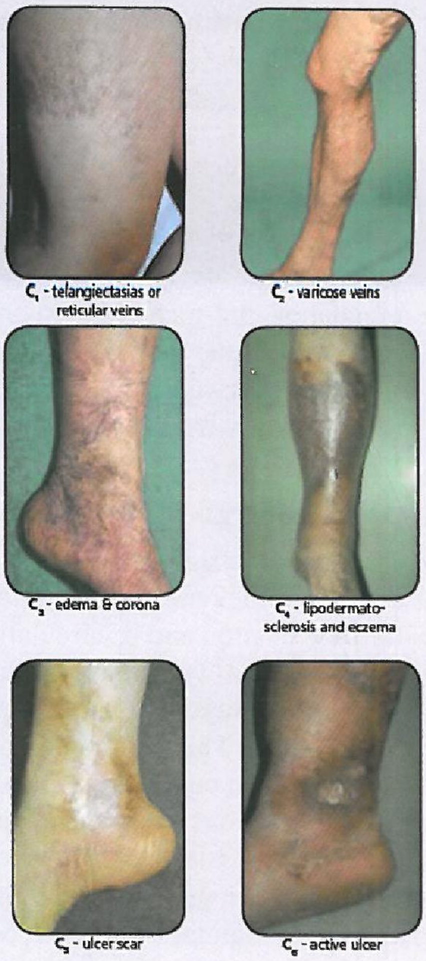
A_S - Superficial veins
A_D - Deep veins
A_P - Perforating veins

Pathophysiology*

P_R - Reflux
P_O - Obstruction

> ***"Early application of compression should be performed to correct swelling and progressive scarring and to initiate the healing process by improving the venous microcirculation."***
>
> Kistner R. Specific Steps to Effective Management of Venous Ulceration. Supplement to Wounds June 2010.

Clinical Classifications with examples



C_1 - telangiectasias or reticular veins

C_2 - varicose veins

C_3 - edema & corona

C_4 - lipodermatosclerosis and eczema

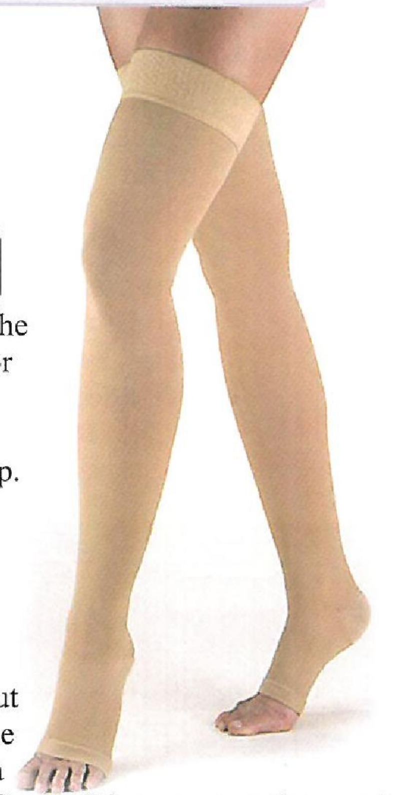
C_5 - ulcer scar

C_6 - active ulcer

*Fronek HS, Bergan JJ, et al. The Fundamentals of Phlebology: Venous Disease for Clinicians. 2004. pg 151.

➢ Management:-

- **Lifestyle modification** *and* **compression therapy**.
- **Control Symptoms** *and* **Complications**
- **Medications (Venoactive drugs; VAD)**.
- **Procedures**.



Lifestyle Modification

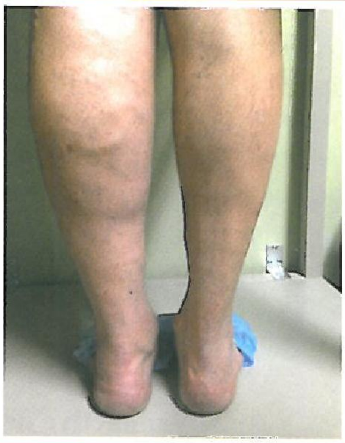
1) **Elevating the legs**; it is important to raise the legs up above the level of the heart to get the maximum effect, and to do this for about a half-hour each time and during sleep.
2) ***W*eight reduction** and ***W*alking**.
3) ***Eat*** a healthy diet high in fiber and low in fat and salt can help.
4) ***Avoid*** long period time *of* traveling.
5) ***Avoid*** chronic constipation, urinary retention or cough.
6) ***Avoid*** wearing tight girdles or belts.
7) ***Avoid*** alcohol.

* **Compression Therapy**;

- Wear compression stockings (*such as* Venosan® - Duomed®); put them in the morning before walking and before the veins become more swollen and remove them at night before going to bed. If a person tries them and experiences worsening pain, especially after walking, remove them and see a health care professional.

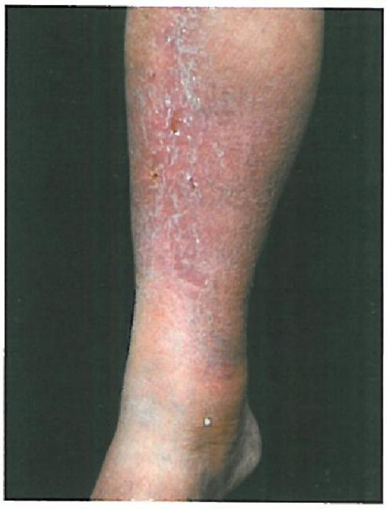
Control Symptoms and Complications

Edema



- *Edema can be temporarily relieved by*;
  1) **Compression therapy**; is the first step in varicose vein management and are effective for treatment of edema.
  2) **Elevating the legs**.
  3) **Venoactive drugs** (*see next; medications*).
  4) **Procedure therapy** (*permanent relief*) (*see next*).
- *Notes*:
  - Leg swelling can vary, it may be swelling at the ankles or full-blown edema.
  - Elevating the legs and wearing compression stockings are often more effective than diuretics in edema, because the swelling is due to vein problems.

Stasis Dermatitis (Varicose Eczema)

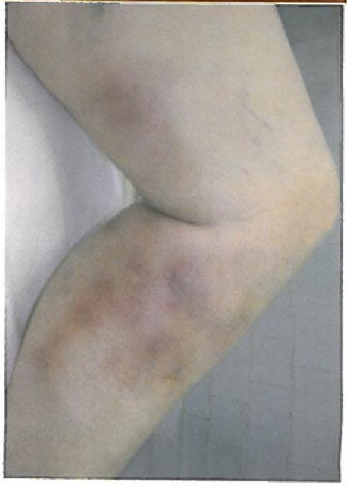


- *Itching can be temporarily relieved by*;
  1) **Topical corticosteroids** & **topical** (or **oral**) **antihistamines**.
  2) **Emollients**.
  3) **Elevating the legs** & **compression therapy**.
  4) **Venoactive drugs**.
  5) **Procedure therapy** (*permanent relief*).
- *Notes*:
  - **Emollients** apply to the skin to ***reduce water loss*** and cover it with a protective film.
  - ***Apply*** **emollient first** and ***wait*** around **30 min**. before ***applying*** the **topical corticosteroid**.
  - ***Using*** a **strong topical corticosteroid** for prolonged periods will ***increase*** the **risk** of **thinning the skin** (use the topical corticosteroid for 7-14 days).

Pain and Inflammation

- *Pain and inflammation can be temporarily relieved by*;
  1) **Topical** (or oral) **non-steroidal anti-inflammatory drugs (NSAIDs)**.
  2) **Elevating the legs** & **compression therapy**.
  3) **Venoactive drugs**.
  4) **Procedure therapy** (*permanent relief*).
- *Notes*: **Oral NSAIDs *should not*** be used for prolonged periods (usually; 7-14 days).

Superficial Thrombophlebitis



- **Superficial thrombophlebitis** is a common inflammatory-thrombotic disorder in which a thrombus develops in a vein located near the surface of the skin.
- It is a **painful** with **erythema**, *often in* a **linear** or **branching configuration** *forming cords*.
- It is generally a benign, self-limited disorder, however, it can be complicated by deep vein thrombosis (DVT) and even pulmonary embolism (PE).
- **NSAIDs** such as **Ibuprofen** or **Aspirin** can be used as part of treatment for superficial thrombophlebitis ***along with*** **compression stockings**.
- In ***extensive*** superficial thrombophlebitis, consideration should be given to **anticoagulant**, **thrombectomy** or **procedure therapy**.

Calcium Dobesilate (Doxium®)

- Calcium dobesilate is a calcium salt of dobesilic acid.
- It is commonly ***used*** in the treatment of **diabetic retinopathy** and **chronic venous insufficiency**.
- It acts on the capillary walls by regulating its impaired physiological functions of resistance and permeability, it reduces plasma and blood hyper-viscosity.
- ***Usual adult dose***; 500-1000 mg once or twice a day with the main meals.

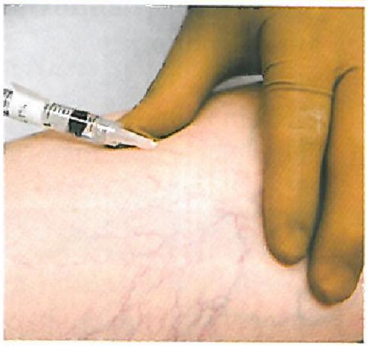
Other Agents

Pentoxifylline (Trental®)

- **Pentoxifylline** [PEN-tox-IF-i-lin] is a methyl-xanthine derivative that ***inhibits*** **phosphodiesterase** enzyme and affects blood rheology.
- It improves blood flow by increasing erythrocyte and leukocyte flexibility. It also inhibits platelet aggregation.
- ***Mechanism of action***; It inhibits erythrocyte phosphodiesterase, resulting in an increase in erythrocyte cAMP activity ⇨ erythrocyte membrane becomes more resistant to deformity. Along with erythrocyte activity, it also decreases blood viscosity by reducing plasma fibrinogen concentrations and increasing fibrinolytic activity. It is also a non-selective adenosine receptor antagonist.
- It is ***used*** in the treatment of **peripheral vascular diseases** and in the **management of cerebrovascular insufficiency**.
- It is ***used*** in patients with **intermittent claudication** due to chronic occlusive arterial disease of the limbs.
- It is ***also effective*** in **venous ulcer** with compression therapy.
- ***Dose***; 400 mg orally 3 times a day.

Procedures

1) Sclerotherapy



- **Sclerotherapy** is a procedure ***used to*** treat spider veins, smaller varicose veins and hemorrhoids ***by injection*** a **sclerosant agent** into the vessels which makes them shrink.
- Sclerotherapy has been used in the treatment of spider veins & occasionally varicose veins for over 150 years by injection of an acid into a vein to induce thrombus formation.
- It's often considered the treatment of choice for small varicose veins.
- The most common sclerosant drugs used are **Polidocanol** or **sodium tetradecyl sulfate**.
- ***Mechanism of action***; after injection ⇨ increasing the formation of blood clots and scar tissue inside veins, this helps decrease dilation, then application of a compression stocking to the vein ⇨ development of fibrosis in the wall of the compressed vein.

Polidocanol *or* Laureth-9 (Aethoxysklerol®) (Asclera®) (Varithena®)

- **Laureth-9** (**Polidocanol**) [LAWR-eth-9] [pol-i-DOE-ka-nol] is a ***sclerosing agent***.
- ***Uses***;
  - Aethoxysklerol®; During sclerotherapy to treat varicose veins (up to 6 mm diameter).
  - Asclera®; During sclerotherapy to treat uncomplicated spider veins (≤1 mm in diameter) and uncomplicated reticular veins (1 to 3 mm in diameter).
  - Varithena®; During sclerotherapy to treat incompetent great saphenous veins, accessory saphenous veins and visible varicosities of the great saphenous vein (GSV) system above and below the knee. Varithena® improves the symptoms of superficial venous incompetence and the appearance of visible varicosities.
- ***Side effects*** (less common); inflammation, blood clot and allergic reaction.

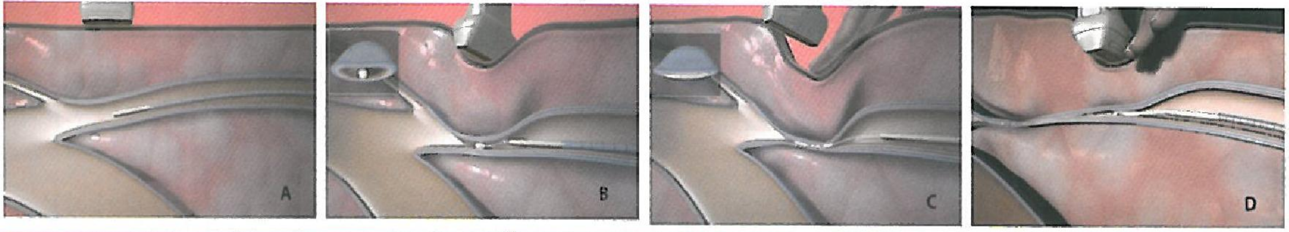
Sodium Tetradecyl Sulfate (Sotradecol®)

- **Sodium Tetradecyl Sulfate** [SO-dee-uhm tet-ra-deck-el] is a ***sclerosing agent***.
- ***Uses***; Treatment of small uncomplicated varicose veins of the lower extremities that show simple dilation with competent valves.
- ***Side effects***; inflammation and allergic reaction.

2) VenaSeal® Closure System

Sapheon
Sapheon

- The **VenaSeal® closure system** is the ***only*** non-tumescent, non-thermal, non-sclerosant procedure.
- It is uses a proprietary **medical adhesive** (cyanoacrylate) delivered endovenously to **close the vein**.
- It is approved by FDA in February, 2015.
- The procedure is administered without the use of tumescent anesthesia, avoiding patient discomfort associated with multiple needle sticks.
- This unique approach eliminates the risk of nerve injury when treating the small saphenous vein, which is a risk sometimes associated with certain thermal-based procedures.
- Clinical studies have demonstrated that the procedure is safe and effective.



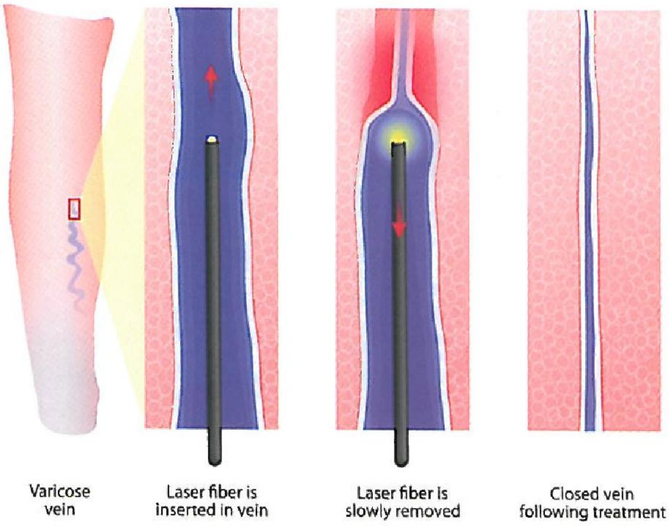
3) Laser Therapy

A) Endovenous laser; used to close off a larger varicose vein, instead of using surgery to remove it.

B) Simple laser; used for small spider veins and tiny varicose veins.

A) Endovenous Thermal Ablation (Endovenous laser)

- **Endovenous Thermal Ablation** (**ETA**) or **Endovenous Laser Thermal Ablation** (**EVLT/EVLA**) or **Endovenous Laser Treatment** (**ELT**), is a technique that uses a laser or high-frequency radio waves to create intense local heat in the varicose vein or incompetent vein ⇨ close the vein.
- It is approved by FDA in 2003.
- Heat is directed through a catheter to close up the targeted vessel. This treatment closes off the problem veins but leaves them in place so there is minimal bleeding and bruising.
- It is a quick, minimally invasive procedure that leaves no scar and can be performed using a local anesthetic.


Varicose vein
Laser fiber is inserted in vein
Laser fiber is slowly removed
Closed vein following treatment

- It is provides better results, involves fewer complications, causes consistently less post-operative discomfort and is much less expensive than surgical stripping (it more expensive in Egypt !!).
- The treatment takes about 20-30 minutes per leg. The patient may also have some foam sclerotherapy and a compression stocking is then put on for 1 week or more.
- ***Complications***;
  - ***Minor***; bruising (51%), hematoma (2.3%), temporary numbness (3.8%), phlebitis (7.4%), induration (46.7%) and a sensation of tightness (24.8%).
  - ***Serious***; skin burns (0.5%), deep venous thrombosis (0.4%), pulmonary embolism (0.1%) and nerve injury (0.8%).

B) Simple Laser

- **Simple laser Therapy**; is a non-invasive light therapy device specifically designed to destroy undesired small blood vessels from all parts of the body.
- It is done on the outside of the skin.
- It effective ***only in*** **spider veins** and **tiny varicose veins**.
- It may be used alone or in combination with Sclerotherapy to maximize treatment results.
- A total of two to three treatments over several weeks may be required to achieve desired results.

4) Surgical Therapy

A) **Stripping**; is used to remove off all or part of large vein in the leg called the superficial saphenous vein.

B) **Ambulatory phlebectomy**; is a minisurgical treatment for superficial varicose veins and so-called side branches.

C) **Vein-ligation**; tying of veins through a small incision in the skin. Ligation may be used in conjunction with vein stripping.

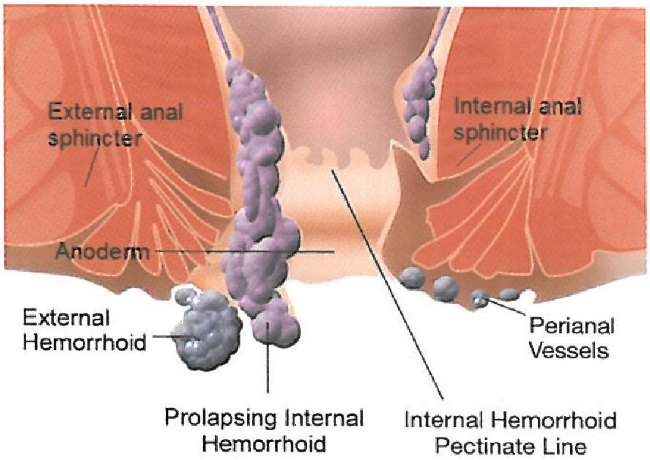
- ***Complication of surgical therapy***; deep vein thrombosis, pulmonary embolism and wound complications including infection.

D) **Cryosurgery**; Cryosurgery is considered a variant of vein stripping. The procedure is surgical and will be performed using a probe. The probe will be introduced in the saphenous vein and then, the surgeon will apply either NO_2 or CO_2 and freeze the vein at temperatures around -85° F (-29.44° C). Once the vein is frozen, the vein can be totally or partially removed.

Hemorrhoids

Definition:-

- **Hemorrhoids** [HEM-uh-roids], also called **piles**; are swollen blood vessels in the lower rectum.
- The first known mention of this affliction is from a 1700 BC Egyptian papyrus.



Prevalence:-

- Symptomatic hemorrhoids are thought to affect at least 50% of the US population at some time during their lives.
- The incidence peak; seems between the ages of 45–65 years.
- Development of hemorrhoids before the age of 20 is unusual, and the risk is higher for whites than for blacks.
- Pregnancy is associated with an increased risk for hemorrhoids, and there is a slightly increased prevalence in women compared with men.
- Chronic constipation has been linked to hemorrhoids.
- Hemorrhoids are commonly seen in patients with spinal cord injury.

Types:-

- Hemorrhoids may be located inside the rectum (**internal hemorrhoids**), or they may develop under the skin around the anus (**external hemorrhoids**).
- However, many people may have a combination of the two.

Signs and Symptoms: Hemorrhoids is **not painful *if* not complicated**.

- *External*;
  - **If thrombosed**; **very painful**, typically resolves in 2-3 days.
  - **Swelling**; may take a few weeks to disappear.
  - **Irritation**; around the anus.
- *Internal*;
  - **Bleeding**; during bowel movement.
  - **Painful**; if thrombosed or necrotic.
  - **Irritation**.
  - **Fecal incontinence**.

Complications:-

- **Anemia**; Due to chronic blood loss.
- **Strangulated Hemorrhoid**; extreme pain and lead to tissue death (gangrene).

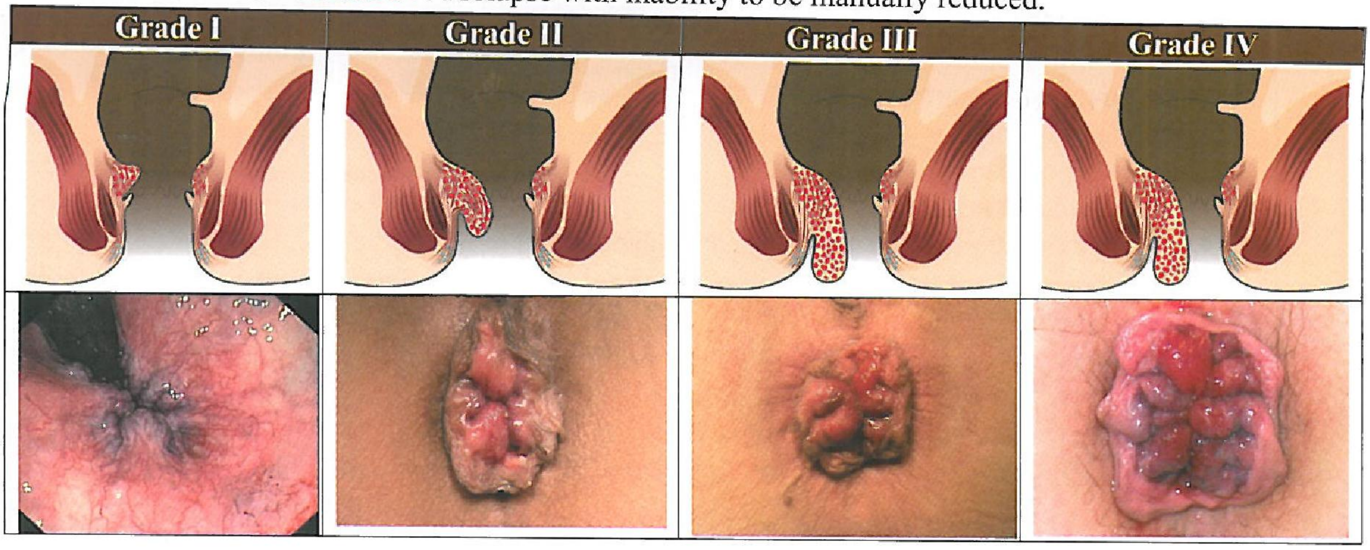
Causes:-

- Veins around the anus tend to ***stretch*** under pressure and may **bulge** or **swell**.
- Swollen veins (hemorrhoids) can develop from an ↑ in **pressure in the lower rectum.**
- Factors that might cause increased pressure ***include***:
  - Straining during bowel movements.
  - Sitting for long periods of time on the toilet.
  - Chronic diarrhea or constipation.
  - Obesity, pregnancy and low-fiber diet.
  - Portal hypertension.

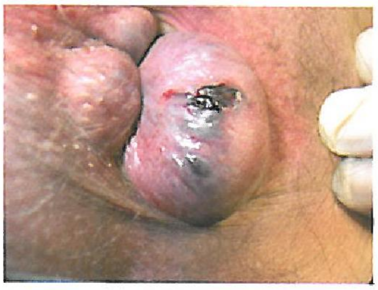
Diagnosis:-

- Hemorrhoids are typically diagnosed by **physical examination**; a **visual examination** of the anus and surrounding area may diagnose external or prolapsed hemorrhoids.

- *Internal*;
  - **Grade I**: No prolapse, just prominent blood vessels.
  - **Grade II**: Prolapse upon bearing down, but spontaneous reduction.
  - **Grade III**: Prolapse upon bearing down requiring manual reduction.
  - **Grade IV**: Prolapse with inability to be manually reduced.

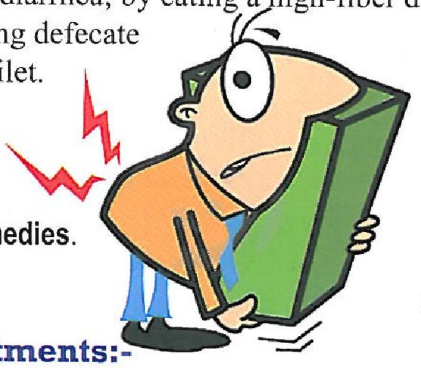


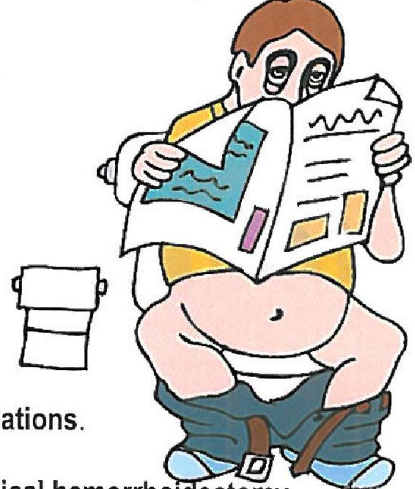
- *External*;
  - External hemorrhoids occur below the dentate or pectinate line.
  - Many anorectal problems, including fissures, fistulae, abscesses, colorectal cancer, rectal varices, and itching have similar symptoms and may be incorrectly referred to as hemorrhoids.



Prevention:-

- Avoid straining during defecate.
- Avoid constipation and diarrhea; by eating a high-fiber diet and drinking enough of fluid.
- Spending less time during defecate
- Avoid reading on the toilet.
- Avoid heavy lifting.
- Weight reduction.





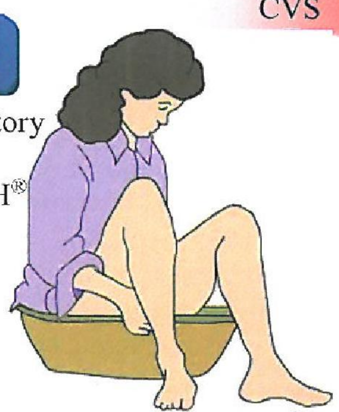
Management:-

- **Lifestyle with Home Remedies.**
- **Medications.**
- **Procedures.**

Quick summary of treatments:-

- Treatment for **internal haemorrhoids** by grade;
  - **Grade I; Lifestyle with home remedies** and **medications.**
  - **Grade II** or **III; Non-surgical procedures.**
  - *Very symptomatic* **grade III** and **grade IV**; **Surgical hemorrhoidectomy.**
- **External haemorrhoids;**
  - **Symptoms; lifestyle with home remedies** and **medications.**
  - **Acute thrombosis; Procedures.**

Lifestyle with Home Remedies



- **Topical treatments**; apply an OTC hemorrhoid cream or suppository containing hydrocortisone or use pads containing witch-hazel (astringent plant extract) or a numbing agent such as Preparation H® cream, suppository, totables or wipes.
- **Sitz bath**; by soaking anal area in plain warm water 10 to 15 min. two to three times a day.
- **Keep the anal area clean**; by shower daily. Avoid soap, it may aggravate the problem. Avoid alcohol based or perfumed wipes.
- **Don't use dry toilet paper**; keep the anal area clean after a bowel movement and use moist towelettes or wet toilet paper that doesn't contain perfume or alcohol.
- **Apply cold**; apply ice packs or cold compresses on the anus to relieve swelling.
- **Take oral pain relievers**; such as short-term use of NSAIDs.

Medications

- **Topical** (or **suppository**) **corticosteroids**; relieve inflammation and itching (should not be used for more than 2 weeks, because they can thin the skin).
- **Topical zinc oxide**, **petroleum jelly**, **cocoa butter**, **hard fat**, **mineral oil** or **shark liver oil**; can prevent further injury and reduce itching by forming a barrier over hemorrhoids.
- **Topical local anesthetic**; can help some people, especially those who have painful external hemorrhoids.
- **Topical Nitroglycerine** and **Diltiazem**; also have been used to relieve symptoms associated with anal sphincter spasm.
- **Topical vasoconstrictor** (**Phenylephrine**) or **astringent** (**Witch-hazel**); reduce pain associated with hemorrhoids by contract swollen veins.

Preparation H®

- Preparation H® was originally developed since 1935. The H simply for "Hemorrhoid".
- Preparation H® which became one of the world's best-selling hemorrhoid treatments.
- The product is sold and manufactured by Pfizer since 2009.
- It is available in several formulation such as; cream, suppository, totables or wipes.
- It contains medications such as that are discussed above.

- **Oral Venoactive Drugs** such as **MPFF** (Daflon®); see page no. 254.
- **Oral NSAIDs**; relieve pain (should not be used for more than 1 week).

Procedures

A) Office-based Procedures;

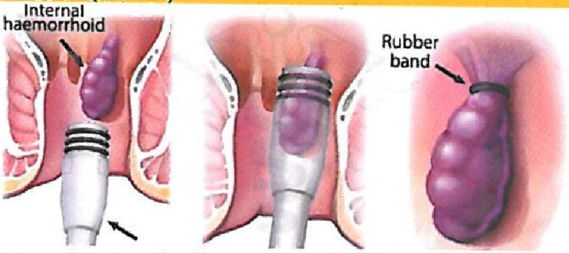
1) **Rubber Band Ligation** (**RBL**).
2) **Sclerotherapy** and **Cryotherapy**.
3) **Coagulation** (**infrared**, **laser** or **bipolar**).

2) Surgical Procedures;

1) **Excisional Hemorrhoidectomy**.
2) **Stapled Hemorrhoidectomy** (**SH**).
3) **Transanal Hemorrhoidal Dearterialization** (**THD**).

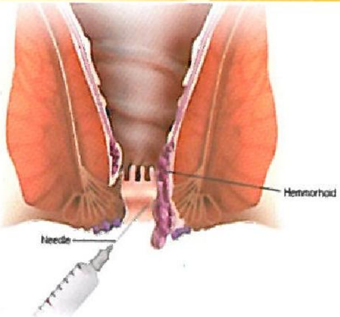
A) Office-based Procedures

1) Rubber Band Ligation (RBL)



- **Rubber band ligation** (**RBL**) is an outpatient treatment for internal hemorrhoids.
- It is typically recommended as the first-line treatment in those with grade 1 to 3.
- It is a procedure in which elastic bands are applied onto an internal hemorrhoid at least 1 cm above the dentate line to cut off its blood supply.
- If the band is placed too close to the dentate line, intense pain results immediately afterwards.
- Within 5-7 days, the withered hemorrhoid falls off.
- Cure rate has been found to be about 87% with a complication rate of up to 3%.
- ***Complications***; Pain (24 to 48) and bleeding (7 to 10 days).
- It is also associated with a recurrence rate that is only 5% at 2 years.

2) Sclerotherapy and Cryotherapy



- **Sclerotherapy** involves the injection of a **sclerosing agent** into the hemorrhoid.
- This causes inflammatory response and as the blood flow into the hemorrhoid is interrupted, secondary fibrosis is facilitated, shrinking the hemorrhoid.
- ***Most common*** **sclerosing agent** in hemorrhoids; 5% phenol in almond oil (PAO) and aluminum potassium sulfate and tannic acid (ALTA).
- The success rate four years after treatment is about 70%.
- The recurrence rate after 2 years was 18.3%, and complications included pyrexia, low blood pressure, perineal pain and rectal ulcers, but those were mild.
- **Cryotherapy**; works by freezing the hemorrhoids, which then fall off or shrinks away.

3) Coagulation

- Coagulation techniques use laser or infrared light or heat.
- Coagulation techniques ***such as***; **Bipolar diathermy coagulation** (**electrotherapy**), **infrared photocoagulation** (**IRC**), **laser therapy** and **radio-wave ablation**.
- **Bipolar diathermy coagulation**; is used for lower-grade hemorrhoids; this technique quickly coagulates the hemorrhoid tissue but has no effect on prolapse.
- **Infrared photocoagulation** (**IRC**); by transforming infrared radiation to heat, which generates sclerosis and fixation of hemorrhoids and used for lower-grade hemorrhoids.
- **Laser therapy**; is more costly and provides no advantage over other methods. Operators must control the laser to avoid bleeding.
- **Radio-wave ablation**; followed by suture ligation could prove to be a safe, cost-effective, and convenient way to treat prolapsing hemorrhoids.

B) Surgical Procedures

1) Excisional Hemorrhoidectomy

- It is a surgical excision of the hemorrhoid used primarily only in severe cases.
- It is associated with significant postoperative pain and usually requires 2-4 weeks for recovery.

2) Stapled Hemorrhoidectomy (SH)

- Occur by circular, hollow tube is inserted into the anal canal, removes a circumferential strip of mucosa about four centimeters above the dentate line. Commonly used in third-degree hemorrhoids.

3) Transanal Hemorrhoidal Dearterialization (THD)

- Occur by a specially developed anoscope combined with a Doppler transducer to identify the hemorrhoidal arteries.
- A suture ligation is performed to effectively decrease the blood flow to the hemorrhoidal plexus.

Revision and Questions
with Answers